SYNTHESIS AND CHEMICAL BEHAVIOR OF STRAINED HALF-CAGE SYSTEMS WITH FUNCTIONAL GROUPS IN CLOSE PROXIMITY

door H.L.E. Depré

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CONTENTS

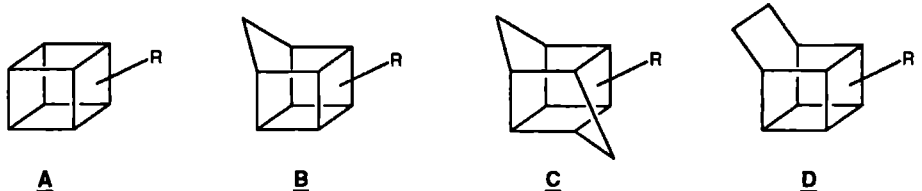
CHAPTER 1

INTRODUCTION

1.1 Eliminative Ring Fission in Bridgehead Cubane Alcohols.

In the past three decades much effort has been devoted to the study of strained polycyclic cage systems[1]. Their structural features, especially their rigidity, the large deformation of the ideal carbon-carbon angles and their sometimes unusual symmetry characteristics make these compounds attractive targets for both synthetic and physical chemists. They provide ideal systems for investigating electronic and magnetic interactions between nonbonded atoms and for studying stereochemical concepts of organic reactions. Regio- and stereocontrolled bond cleavages within these polycyclic systems may lead to synthons for pharmaceutically and biologically interesting molecules[2].

In the Department of Organic Chemistry at the University of Nijmegen, strained cage systems have been a subject of interest since the early seventies. Most of the efforts were focussed on the synthesis and chemical properties of bridgehead substituted cubanes **A**, homocubanes **B**, bis-homocubanes **C** and basketanes **D** [3]. In particular, the synthesis and chemical behavior of

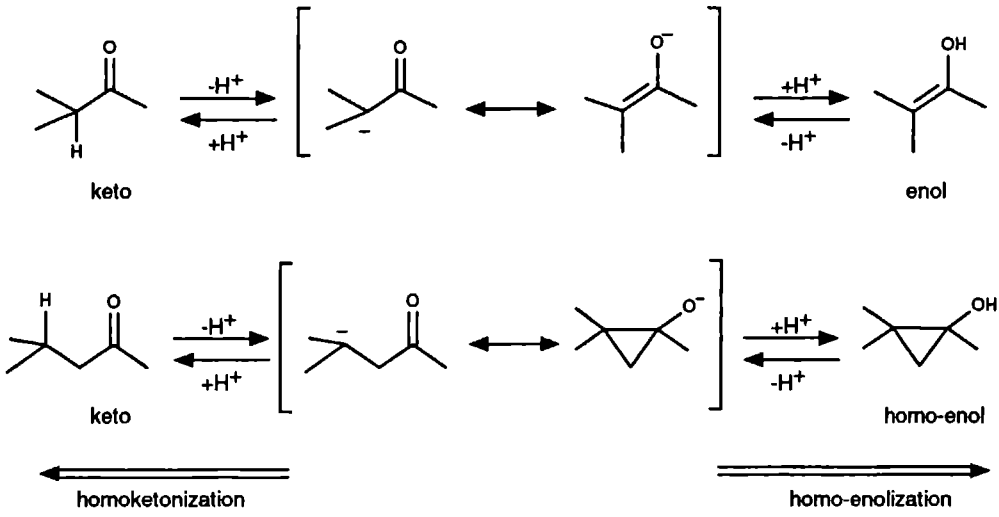


A **B** **C** **D**

bridgehead cage alcohols and their derivatives was investigated. These alcohols are usually extremely sensitive to base to give a selective cage opening reaction, *viz.* a homoketonization reaction. The concept of homoketonization, which was introduced by Nickon *et al.*[4], is depicted in Scheme 1.1. The reverse process is homoenolization. The principle of homoenolization-/homoketonization is similar to that of keto-enol tautomerization in carbonyl compounds, however instead of the involvement of an α-proton in the initial enolization process, a proton at a remote position, *e.g.* a β, γ, δ proton, is now abstracted. The resulting carbanion can now be stabilized by orbital interaction with the π-electron system of the carbonyl function. Depending on the geometry and size of the cyclic homoenolate thus formed, such an interaction, named as homoconjugation, may lead to stabilization. If so, protonation of the homenolate leads to an alicyclic alcohol which may also be denoted the homo-enol. The reverse process, the base-induced ringopening of this cyclic alcohol is called homoketonization[5].

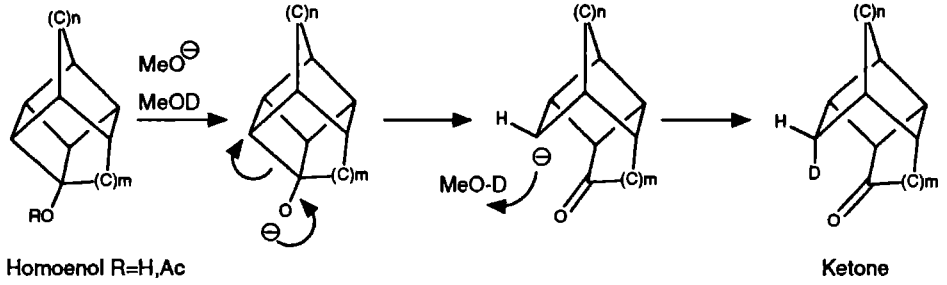
The homoketonization reaction of highly strained cubane-type bridgehead alcohols appeared

Scheme 1.1



to be a regio- and stereospecific process leading to the exclusive formation of the thermodynamically most stable half-cage ketones with retention of configuration (*endo*-protonation) (Scheme 1.2)[3]. This

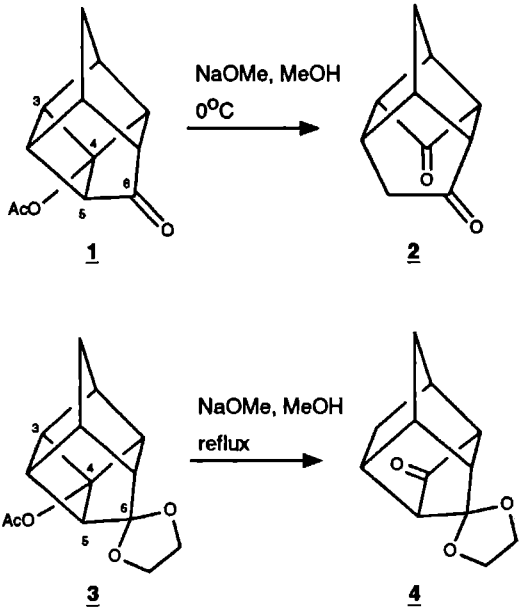
Scheme 1.2



striking selectivity is best explained by assuming that the product-developing stage is located rather late on the reaction coordinate and therefore is strongly influenced by the thermodynamic stability of the product. This assumption implies that protonation only takes place after the development of considerable charge density on the leaving C-atom.

A contra-thermodynamic cage opening in the 1,3-bishomocubane system was realized by attaching a carbanion stabilizing group at one of the two conceivable nucleofugal carbon atoms that would not afford the thermodynamical most stable half cage ketone[3,6]. Mild treatment of ketone acetate **3** with sodium methoxide in methanol at 0°C gave an almost instantaneous cage-opening reaction to afford the C_4-C_5 cleavage product **2** in quantitative yield (Scheme 1.3). The acetal acetate

Scheme 1.3

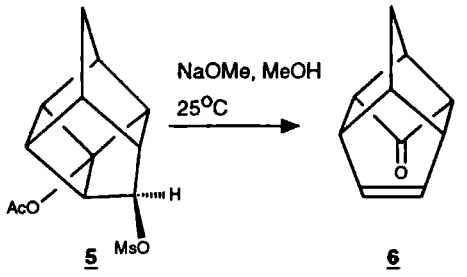


3, however, underwent base-induced homoketonization to produce the C_3-C_4 cleavage product **4**. In both cases the one-bond cleavage proceeds with retention of configuration. The regiochemistry attained for the opening of the acetal acetate **1** conforms entirely to the general pattern observed for the non-activated nucleophilic eliminative ring-fissions of strained cage bridgehead acetates, *i.e.* producing the thermodynamically most stable half-cage ketone. The product obtained in the homoketonization of ketone acetate **1** is, according to MM2-calculations, thermodynamically the least stable one among the three possible half cage ketones[7]. The formation of this 'contra-thermodynamic product' convincingly demonstrates that conjugative stabilization of the nucleofugal carbanion is sufficient to overrule the aforementioned thermodynamic control during ring opening of the 1,3-bishomocubane cage system.

A 'contra-thermodynamic' cage-opening reaction could also be enforced by a 1,3-through-cage elimination reaction in bridgehead cage acetate (or alcohol) **5** (Scheme 1.4)[8]. Treatment of mesylate **5** with sodium methoxide in methanol at room temperature for a few minutes gave enone **6** in excellent yield. It should be noted that this cage cleavage reaction only takes place when the mesylate has the *anti*-configuration as shown for **5**. The corresponding *syn*-mesylate only leads to methanolysis of the acetate ester to form the bridgehead alcohol. This difference in behavior of the syn- and anti-compound proves that the 1,3-through-cage elimination process is subject to a strict stereoelectronic control resembling a Grob-type elimination reaction which requires that the leaving group and the bond to be cleaved are in a trans-antiparallel orientation[9].

The tetracyclic enone **6** is an interesting structure since it contains two isolated orthogonal

Scheme 1.4

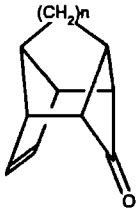


5 6

π-electron systems in close spatial proximity. According to MM2-calculations[10] the distance between the carbonyl carbon and the olefinic carbon is 2.73-2.86 Å, showing that both functionalities are within their Van der Waals distances. Indications for non-bonded interactions between these π-systems were obtained from the UV-spectrum of **6** which shows an absorption at 200 nm (hexane)[7]. Compound **6** still contains a considerable amount of strain energy which according to the above calculations amounts to 55 kcal/mole. These structural features together with its high rigidity make enone **6** an attractive subject for further studies. Moreover, molecular modeling shows that extension of the C_6-methylene bridge to a ethylene or propylene bridge leads to a decrease of the interatomic distance between the ketone and the olefinic function and a concomitant increase of strain energy (Figure 1.1). This strain effect is probably due to enforced proximity between the electronegative carbonyl oxygen and the olefinic double bond. The difference in proximity of these functionalities may be reflected in the chemical properties of these half-cage structures.

Figure 1.1

MM_2 calculation of carbonyl brendenes **6**, **7** and **8**



		strain energy (kcal/mole)	distance* (Å)
6	(n=1)	65.1	2.73
7	(n=2)	70.7	2.61
8	(n=3)	82.7	2.54

*distance between the carbonyl carbon atom and a carbon atom of the olefinic function

1.2 Nomenclature of cage compounds.

The cage compounds described in this thesis will be denoted in the text mainly by their trivial names. In the experimental section however their systematic names will be used according to the nomenclature rules of the IUPAC[11]. These rules are:

1) The prefixes bicyclo, tricyclo etc. indicate the number of bonds that has to be broken in a given polycyclic system to get an open aliphatic hydrocarbon.
2) The largest possible carbon ring in the molecule is considered the main ring.
3) The main bridge is the longest chain of atoms that spans the main ring. Are there more carbon bridges with an equal number of atoms, then that bridge will be taken which divides the main ring as symmetrical as possible.
4) The main ring, spanned by the main bridge, forms a bicyclic system, which will be numbered in the usual manner. Starting point should be a bridgehead atom and then proceed along the largest bridge followed by the next largest one.
5) The other bridges will be indicated by extra numbers provided with small indices, representing the number of atoms in the bridge and the connecting atoms in the main ring, respectively. When there is the possibility for more than one systematic name, the name with the lowest indices will have priority.
6) Finally, the suffix butane, pentane etc. denotes the number of atoms which are being used for constructing the polycyclic framework.
7) Functional groups attached to the polycyclic system are indicated by their connecting number to the main ring and their name as dictated by the IUPAC nomenclature rules.

When the above rules are applied to alkenone **6** (Scheme 1.4) the following results are obtained:

Rule 1: The prefix will be tetracyclo, since four bonds have to be broken to give an open aliphatic compound.

Rule 2: The largest possible ring (the main ring) in alkenone **6** is cycle **A** (Figure 1.2)

Rule 3: Since all ten skeletal carbon atoms of **6** can be included in the main ring the remaining bridges contain no carbon atoms and therefore are called zero-bridges. The bridge that divides the main cycle as symmetrical as possible is now introduced. For **6** the main bridge is the zero-bridge between C_1 and C_7 (Structure **B** in Figure 1.2)

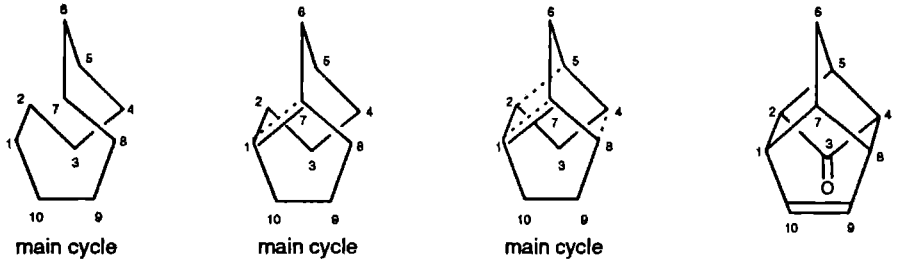
Rule 4: The bicyclic structure **B** now constitutes a bicyclo[5.3.0] system.

Rule 5: To complete the construction of compound **6** another two zero-bridges have to be drawn in **B**, *viz.* between C_2 and C_5, and between C_4 and C_8. These bridges are denoted $0^{2,5}$ and $0^{4,8}$, respectively. By adding these bridges to the bicyclic system [5.3.0] a tetracyclic system is obtained. The skeleton is now completely described by the notation: tetracyclo[$5.3.0.0^{2,5}.0^{4,8}$] (Structure **C** in Figure 1.2).

Rule 6: The skeleton of **6** contains 10 atoms which are all carbons (this is, however, not a requirement) and therefore this alkenone is denoted a decane. Hence the unsubstituted skeleton of **6** is named: Tetracyclo[5.3.0.$0^{2,5}$.$0^{4,8}$]decane.

Rule 7: Finally, the substituents are added to the name. Depending on the priority rules that are valid for functional groups the eventual ring numbering may be affected. In this particular case the carbonyl function has the highest priority and therefore should have the lowest possible number. Since the numbering should start at one of bridgehead positions of the bicyclic system obtained under Rule 4 (structure **B**) there are in principle two ways around *viz.* starting at position 1 and then proceeding along the largest bridge or starting at position 7 and move around the same five carbon bridge. In the first case the ketone function will obtain the number 3 whereas in the other case the ketone function will have number 5. It is evident that the numbering as given in structure **B** is the correct one. This leads then to the following systematic name for alkenone **6**: Tetracyclo[5.3.0.$0^{2,5}$.$0^{4,8}$]deca-9-en-3-one.

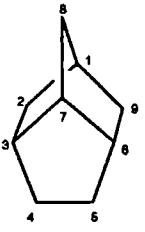
Figure 1.2



Since systematic names are not always practical in both verbal and written discussions trivial names are often introduced for these polycyclic structures. The trivial name designed for alkenone **6** is based on the trivial name *brendane* given by Nickon *et al.*[12] to compound **9** that closely resembles **6** (Figure 1.3). By adding a C=O unit between the C_2 and C_9 in **9** the basic skeleton of enone **6** is obtained, *viz.* **10**. According to the IUPAC rules such a C=O unit should be denoted *carbonyl*. This leads directly to the trivial name of ketone **10** as 2,9-carbonyl-brendane. Having constructed the basis framework of **6** the original brendane numbering should be followed. Introduction of the alkene moiety therefore leads to 2,9-carbonyl-brend-4-ene as the trivial name for **6**.

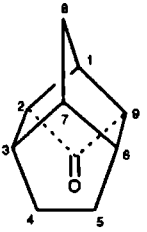
Other trivial names given in this thesis are also based on the brendane skeleton, *viz.* 2,9-carbonyl-1,8-homo-brend-4-ene for **7** and 2,9-carbonyl-1,8-bishomo-brend-4-ene for **8** (Figure

Figure 1.3



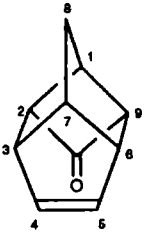
brendane

9



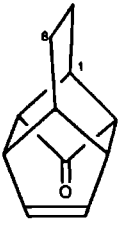
2,9-carbonyl-brendane

10



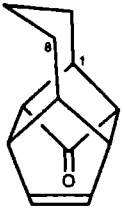
2,9-carbonyl-brend-4-ene

6



2,9-carbonyl-1,8-homo-brend-4-ene

7



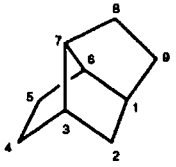
2,9-carbonyl-1,8-bishomo-brend-4-ene

8

1.3). The structures **7** and **8** are homologues of **6** and differ only from **6** in the size of the bridge that spans C_1 and C_7.

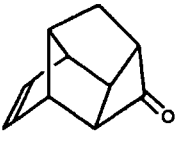
Another series of trivial names used in this thesis is based on the brexane skeleton **11** (Figure 1.4). This name was also introduced by Nickon *et al.*[12] and is related to brendane. Both structures can be readily interconverted at least in principle. This relation also holds for the tetracyclic ketones **12** and **13**, which are the rearrangement products of **6** and **7**, respectively (Chapter 3 of this thesis). Based on the same reasoning as above ketones **12** and **13** are now named as 2,9-carbonyl-brex-4-ene and 2,9-carbonyl-1,9-homo-brex-4-ene (Figure 1.4).

Figure 1.4



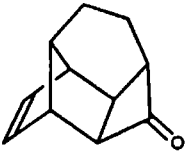
brexane

11



2,9-carbonyl-brex-4-ene

12



2,10-carbonyl-1,9-homo-brex-4-ene

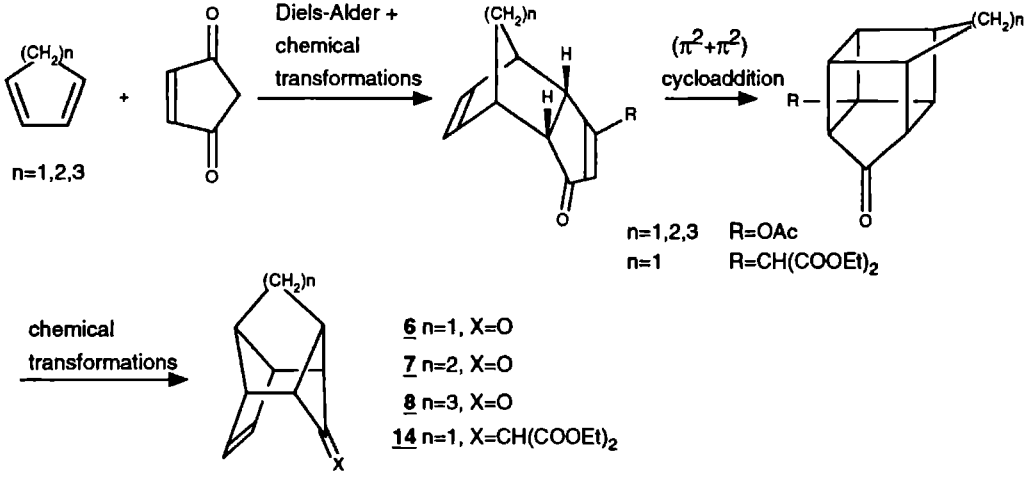
13

1.3 Aim and outline of this thesis.

The aim of the research described in this thesis is to explore the chemistry of 2,9-carbonyl-brend-4-ene **6** and its homologues **7** and **8**. These half-cage systems are unique structures as they are highly strained and contain two π-systems in close proximity and constrained in a rigid framework. The impact of both features on the chemical reactivity of carbonylbrendenones and their derivatives are the major subject of this thesis.

Chapter 2 deals with the syntheses of compounds **6**, **7**, **8** and **14**. All these half-cage structures are accessible by applying three principal steps: (i) synthesis of an appropriately substituted precursor, the so-called photoprecursor; (ii) subsequent $[\pi_2+\pi_2]$-photocyclization of the photoprecursor to form the basic cage skeleton; (iii) modification of the cage compound thus obtained to give the desired structures (Scheme 1.5). An analysis of the observed spectral data is given in view of possible interaction between the two orthogonal π-functions.

Scheme 1.5

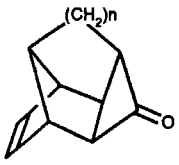


Chapter 3 deals with the chemical properties of compounds **6** and **7**. Reactions that will be discussed are:

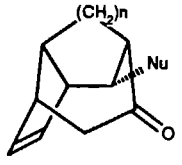
- Acid catalyzed rearrangements affording products **15**, **16** and **17**.
- Additions of organometallic reagents (RLi, RMgX) and hydrides leading to alcohols of type **18** and **19**.
- Electron-transfer type reductions (Li in NH_3) which for **6** leads to tricyclic alcohol **20**.
- Nucleophilic additions such as the addition of hydrazine which for **7** gave rise to the formation of bicyclic hydrazide **21**.
- The Wittig and Peterson reaction in order to obtain the corresponding diene systems **22**.
- The hydrogenation of **6** in order to obtain **23.**

- Bromination; that for 7 leads to the rather complex lactone 24.
- The reaction with diazomethane affording heterocyclic compounds of type 25.

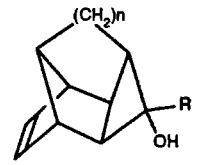
In chapter 4 the chemical behavior of alcohols 19 which are readily available from enones 6 and 7 will be discussed. The base-induced intramolecular nucleophilic addition of the hydroxylic function at the non-activated olefin function leading to oxa-cage compounds 26 is analyzed in terms of interatomic distances (proximity effect) and strain.



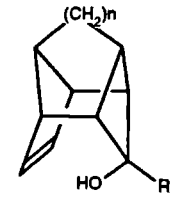
15 n=1
16 n=2



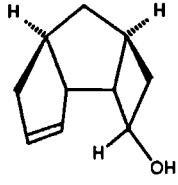
17 Nu = Cl and n = 1
Nu = Br and n = 1+2
Nu = OMe and n = 2



18 $R=CH_3$ and n=1+2
$R=CH_2Si(CH_3)_3$ and n=1



19a R=H and n=1+2
b $R=CH_3$ and n=1+2
c R=nBu and n=1+2
d R=Ph and n=1+2



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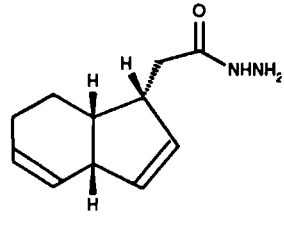

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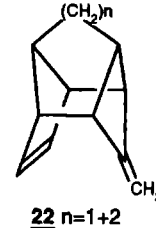
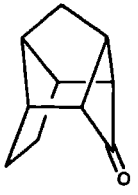


22 n=1+2



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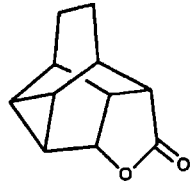

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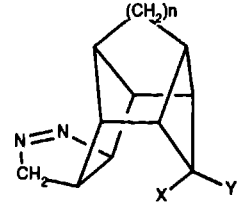
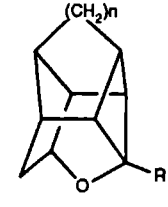


25 X=Y=O; n=1+2
X=OH, Y=H; n=1+2
X=OAC, Y=H, n=1+2



26 n=1+2

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SYNTHESIS OF 2,9-CARBONYL-4-BRENDENES, STRAINED HALF-CAGE SYSTEMS WITH ORTHOGONAL Π-BONDS IN CLOSE PROXIMITY

2.1 Introduction

The synthesis of cubane-type strained polycyclic compounds usually involves a sequence of three principal steps, *viz. (i)* photocyclization via an intramolecular [$\pi^2+\pi^2$] cycloaddition as the key step, *(ii)* preparation of the precursor for this photoreaction, *(iii)* modification of the initially formed cage compound. The above strategy was successfully applied for the synthesis of cubane by Eaton and Cole[1] in 1964. From this time on, many chemists investigated the synthesis and chemical behavior of related strained polycyclic systems[2].

The research program on cage compounds in the Department of Organic Chemistry of the University of Nijmegen is particularly aimed at the synthesis of strained cubane related cage structures functionalized at bridgehead positions in order to establish the relationship between their chemical reactivity and cage strain energy[3]. In this context strained bridgehead alcohols and their esters have been extensively studied[3]. Both under basic and acidic conditions these structures may undergo regio- and stereoselective nucleophilic eliminative ring fissions in which a carbonyl function is formed by elimination of a carbon leaving group. It was shown that such a ring fission may lead to the interesting strained tetracyclic alkenone **1** in which two isolated orthogonal π-systems are in close proximity[4]. The observation of a maximum absorption in its ultraviolet spectrum at 204 nm (hexane ϵ 3200), which may be indicative of orbital-orbital interaction between the two π-systems in **1**, was a reason to investigate the chemistry of this type of half-cage structures in more detail.

Table 1

MM_2 calculation of carbonyl brendenes **1**, **2** and **3**

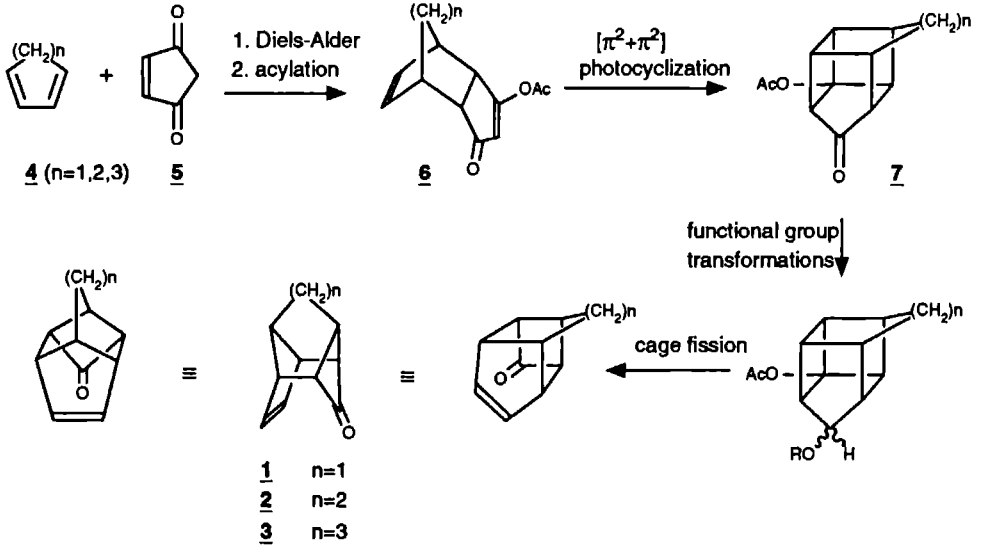
		strain energy (kcal/mole)	distance* (Å)
1	(n=1)	65.1	2.7
2	(n=2)	70.7	2.6
3	(n=3)	82.7	2.5

*distance between the carbonyl carbon atom and a carbon atom of the olefinic function

This chapter deals with the synthesis and structural properties of a series of 2,9-carbonyl-4-brendenes, viz. 1, 2 and 3. These structures differ only in the size of the carbon bridge which spans the four- and five membered ring contained in these systems. Molecular mechanic (MM2) calculations reveal considerable influence on the geometry of the basic tetracyclic system when the methylene bridge in 1 is replaced by a larger unit, such as a two-carbon or a three-carbon bridge (Table 1). The total ring strain notably increases for 2 and 3 when compared with 1, while at the same time the olefin and carbonyl function are coming in even closer proximity. These data suggest that for all three compounds, especially for 2 and 3, an interesting interaction between both π-functions may be expected.

For the synthesis of the carbonyl brendenes 1, 2 and 3 essentially the methodology for the formation of strained cage compounds, as mentioned above, can be applied. A regioselective through-cage elimination[4] completes this route. The sequence of events is depicted in scheme 1.

Scheme 1

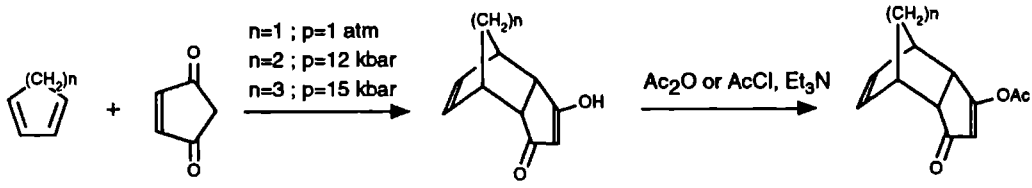


2.2 Results and Discussion

2.2.1 Synthesis of photoprecursors 6 by a Diels-Alder reaction of cyclopenten-1,4-dione and cyclic dienes

The synthesis of photoprecursors 6 can be achieved by a Diels-Alder reaction of cyclopenten-1,4-dione 5 and appropriate cyclic dienes 4 (Scheme 2). Cyclopentadiene is a reactive

Scheme 2



4a n=1 **5** **8a** (75-85%) **6a** (82%)
4b n=2 **8b** (70-80%) **6b** (78%)
4c n=3 **8c** (20-30%) **6c** (80%)

diene because of its planar cisoid conformation and the preparation of tricyclic adduct **8a** is therefore readily achieved on multigram scale by simply stirring dione **5** and excess of diene **4a** at room temperature in benzene or toluene[5] at atmospheric pressure.

With 1,3-cyclohexadiene Diels-Alder reactions usually proceed slower than with cyclopentadiene. For instance, the Diels-Alder reaction of diene **4b** with maleic anhydride proceeds 12 times slower than with cyclopentadiene[6]. Furthermore, cyclopenten-1,4-dione is four times less dienophilic than maleic anhydride[5]. Therefore, a rather slow reaction for diene **4b** and dione **5** is expected. In fact, after a reaction time of 4 weeks at room temperature and atmospheric pressure only a moderate yield (40%) of adduct **8b** could be obtained. In order to improve the yield of this Diels-Alder reaction high pressure was employed. It is well documented that Diels-Alder reactions benefit from high pressure[7]. In the case of diene **4b** and dione **5**, which were used in the ratio of 2.5:1, the cycloaddition was carried out at a pressure of 12 kbar in a solvent mixture of toluene and benzene (9:1) at room temperature, yielding the desired adduct **8b** in 85%. It should be noted that a radical inhibitor, (*i.c.* hydroquinone), must be added to avoid undesired side reactions. A drawback of the high pressure technique is that hitherto the scale of the reaction is rather limited (2.5 g per run).

1,3-Cycloheptadiene is far less reactive than the six-membered cyclic diene **4b**. This is attributable to the larger ring size and the severe non-bonded interaction of the methylene groups in a planar structure. As a result the double bonds no longer adopt the necessary coplanar configuration[8]. By performing the Diels-Alder reaction of diene **4c** and dione **5** at 12 kbar adduct **8c** was obtained in a yield of circa 5%. Employing an excess of **4c** (ratio **4c**:**5** = 2.5:1) and using a toluene/benzene (5:1) solvent mixture, adduct **8c** was obtained in a maximum yield of 20-30% when the reaction was carried out in the presence of a radical inhibitor at a pressure of 15 kbar. Under these conditions a considerable amount of a polymer of cycloheptatriene was produced as well. For practical reasons adduct **8c** was converted into its acetate **6c** without purification.

Cycloadducts **8a** and **8b** both have the *endo*-enol structure as was deduced from their ^{1}H-NMR spectral features (three olefinic protons and a broad resonance for the alcoholic proton).

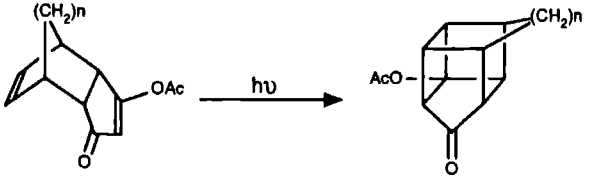
Because of the presence of large amounts of cycloheptadiene polymer, NMR spectroscopy did not allow such a conclusion for adduct **8c**.

The cycloadducts **8** as such are not suitable as photoprecursors as they do not undergo photocyclization[4]. Conversion into their acetates **6** is therefore required. Treatment of the enols **8** with acetic anhydride or acetyl chloride in the presence of a base, readily gives the corresponding acetates in good yields[4,9] (Scheme 2). It should be mentioned, however, that a prolonged reaction time causes considerable loss of yield.

2.2.2 Cyclization of the photoprecursors 6

The key step in the synthesis of strained cage compounds **7**, *viz.* the intramolecular ($\pi^2+\pi^2$) photocyclization of tricyclic precursor **6**, proceeds smoothly in all three cases (Scheme 3). Enol

Scheme 3



6a n=1 (methanol) **7a** (96%)
6b n=2 (benzene) **7b** (97%)
6c n=3 (benzene) **7c** (55%)

acetate **6a** gave an almost quantitative yield of **7a** upon irradiation in methanol. This high yield implies that Diels-Alder adduct **8a** (scheme 2) must have the *endo* structure. Similarly, enol acetate **6b** produces cage compound **7b** in an almost quantitative yield, provided that benzene or ethyl acetate is used as the solvent. Irradiation of **6b** in methanol leads to some side products as was indicated by GLC analysis of the crude photoproduct. Enol acetate **6c** could also be converted into cage compound **7c** in good yield using benzene as the solvent. The time of irradiation necessary to give complete conversion into **7c** was considerable longer than in the other two cases.

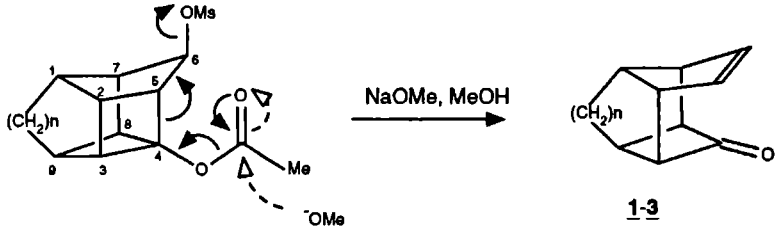
A comparison of reaction times was made for the conversion of 10 g of the respective photoprecursors. For **6a** 10 h were necessary to complete the cage closure, while for **6b** about 22 h and for **6c** about 160 h were needed. This difference in reaction time for the photocyclization can be attributed to the increased ring strain going from **7a** to **7c**. Moreover, the two double bonds involved in the closure reaction will have a less parallel orientation with respect to each other when the size of the bridge in **6** is increased. For an efficient [$\pi^2+\pi^2$] photocycloaddition the olefinic bonds should

preferably be positioned parallel, as was already pointed out by Osawa[10].

2.2.3 Through-cage elimination to carbonyl brendenes 1-3

The final operation in the synthetic sequence to carbonyl brendenes **1**, **2** and **3** is a bond cleavage reaction in the cage compounds **7**. For this purpose a Grob-type elimination is used. First, the carbonyl function in the photocyclization products **7** must be converted into a mesyloxy group to provide the required leaving group. It should be noted that the Grob elimination is subject to stringent stereoelectronic control[11], *viz.* the leaving group (i.e. the mesyloxy group) should have a trans anti-periplanar position with respect to the C_4-C_5 bond in the cage compound, the bond that will be cleaved during the elimination reaction (Scheme 4).

Scheme 4



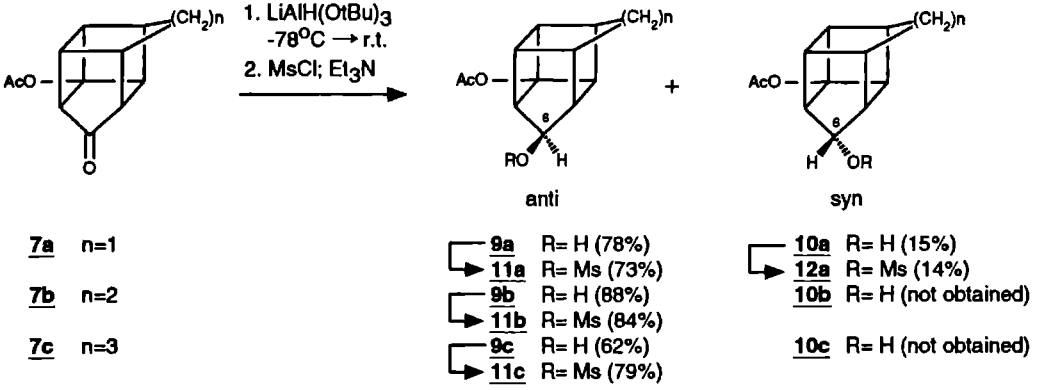
1-3

The carbonyl group in photoproducts **7** could selectively be reduced with either sodium borohydride in methanol or lithium tri-*tert*-butoxyaluminumhydride in ether at room temperature. In a subsequent step the resulting alcohols were converted into the corresponding mesylates (Scheme 5). In either case the sensitive acetate function at the bridgehead was unaffected. Cage ketone **7a** gave a mixture of the epimeric alcohols **9a** and **10a** in the ratio of 3.5:1 in total yields of 60% with sodium borohydride in methanol and 80% with lithium tri-*tert*-butoxyaluminumhydride in ether. An improved yield of the desired epimer **9a** could be realized by gradually adding cage ketone **7a** to a lithium tri-*tert*-butoxyaluminumhydride suspension in ether at -78°C. In this manner a total yield of 93% was obtained with an epimeric ratio of 5:1 (Scheme 5).

In the ^{1}H-NMR spectra of the mixture of **9a** and **10a** the epimeric H_6 protons appear as two distinct somewhat broadened singlets at δ 4.15 and δ 4.4 ppm allowing a simple and accurate determination of the epimeric ratio. The epimeric mesylates **11a** and **12a** could be separated by repeated crystallization from methanol. The structure of epimer **11a** was secured by means of an X-ray diffraction analysis[4].

The reaction of keto acetates **7b** and **7c** with a lithium tri-*tert*-butoxyaluminumhydride suspension in ether was stereospecific and led exclusively to the *anti* epimers **9b** and **9c**,

Scheme 5

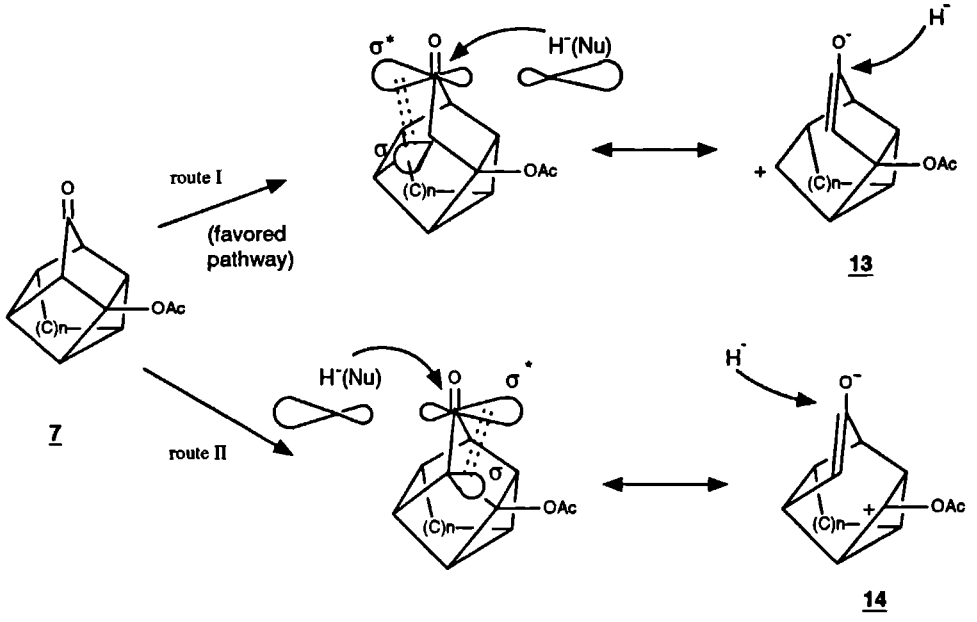


respectively, in yields of 88% and 62% when performed at -78°C (Scheme 5).

The stereochemistry of the reduction of cage ketones **7** deserves some further comment. On merely steric grounds one would expect that for one face of the carbonyl group the attack of the hydride donating agent is hampered by the acetate function, thus leading to *syn* epimer **10**. On the other hand, initial complexation of the reducing agent with the acetate function can be envisaged, which would lead to a preferential formation of the *anti* epimer **9**. In addition, electronic effects may play a role, *viz.* involvement of hyperconjugative effects in the face selection of this reduction process[12], similar to the control during nucleophilic reactions of adamantanone with a substituent X which is four σ bonds removed from the carbonyl function[13]. When this group X is electron withdrawing preferential formation of the *anti* product is observed, while for X being electron donating the opposite stereochemistry is found. According to the Cieplak theory[12], the nucleophilic reaction with the carbonyl group results in the development of a σ* orbital which can interact with a nearby parallel electron-rich σ bond. In the most extreme case one can postulate a cationic resonance structure, which is stabilized or destabilized by the group X depending on its nature. This Cieplak theory of transition state hyperconjugation has been successfully applied to account for the stereochemistry of a large variety of additions reactions[14]. In the present case of keto acetates **7** the Cieplak theory involves the extreme cationic resonance structures **13** and **14**, of which **13** will be favored as in this structure the destabilizing acetate function is not attached to the cationic center (Scheme 6). Therefore, this hyperconjugative effect favors the *anti* epimer. This epimer is also expected on the basis of coordination of the reducing agent with the acetate group. Both effects apparently work in the same direction.

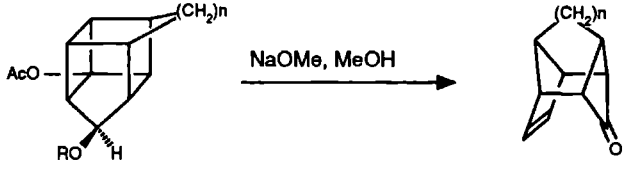
The final step in the synthesis of carbonyl brendenes is the through-cage elimination reaction. Treatment of the mesylates **11** (all having the *anti* configuration) with sodium methoxide in

Scheme 6



methanol at room temperature resulted in the smooth formation of carbonyl brendenes **1**, **2** and **3**, respectively, in good yields (Scheme 7). Attack of the methoxide ion at the acetate function by an

Scheme 7



11a
11b
11c

1 (81%)
2 (77%)
3 (65%)

addition-elimination reaction, clearly initiates the through-cage elimination in the manner shown in Scheme 4. The need for the *anti* configuration of these substrates is convincingly demonstrated by the reaction of *syn* mesylate **12a** with base. Only solvolysis of the acetate to a free hydroxyl group could be achieved. No through-cage elimination was observed, even not under enforced conditions. The carbonyl brendenes **1**-**3** can be purified by flash column chromatography, whereby removal of the eluent should be performed with great care in view of the volatility of these products.

2.2.4 Spectral features of carbonyl brendenes: The quest for intramolecular interaction.

The structures of the carbonyl brendenes were established by means of spectroscopy. Characteristic are the relative simple ^{1}H- and ^{13}C-NMR spectra, due to the high degree of symmetry of these molecules. The ^{1}H-NMR spectra ($CDCl_3$) show the olefinic protons at δ 6.15, δ 6.48 and δ 6.62 ppm for 1, 2 and 3, respectively. The signals of the bridge protons appear as narrow signals between 2.1 and 1.6 ppm. The remaining six cage protons are observed as narrow multiplet signals between 3.2 and 2.2 ppm. The ^{13}C-NMR spectra ($CDCl_3$) show, because of the symmetry plane in the carbonyl brendenes, m-3 carbon signals (m = number of carbon atoms in 1, 2 and 3) among which the ^{13}C=O at δ 199.7, δ 200.4 and δ 197.9 ppm for 1, 2 and 3, respectively. Both the position of the ^{13}C=O resonance in the ^{13}C-NMR spectra and the relatively high C=O absorption in the IR spectra at 1769, 1764 and 1755 cm^{-1} for 1, 2 and 3, respectively, proves the presence of a cyclobutanone.

The objective of this study is to uncover a possible interaction of the orthogonal π-bonds in close proximity. As indicated by MM2 calculations (see Table 1), increasing the size of the bridge will enhance the ring strain and bring both π bonds closer to each other. The question is whether such effects are observable in the respective spectra.

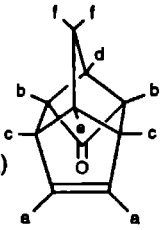
The ^{1}H-NMR data of 1, 2 and 3 are collected in Table 2. The olefinic protons clearly show a shift to lower field going from 1 to 3. This observation can be explained in two ways. First, closer proximity of the carbonyl group will cause an enhanced interaction with the olefinic bond resulting in a lower electron-density at the olefinic carbon atoms which in turn affects the chemical shift of the olefinic protons in the downfield sense. Alternatively, local strain due to the increasing size of the bridge going from 1 to 3, will result in an olefinic bond with an increasing "cyclobutene" character (cylopentene: $\delta_{olefine}$= 5.6 ppm; cyclobutene: $\delta_{olefine}$= 5.97 ppm.)[15], which also causes a downfield shift.

The ^{13}C-NMR signals of the olefinic carbon atoms exhibit a similar trend as those of the olefinic protons, namely a downfield shift in going from 1 to 3 (see Table 2). This observation can be explained by the same phenomena as suggested for the olefinic proton shifts, *viz.* interaction with the carbonyl and/or local strain due to the increasing size of the bridge.

The carbonyl absorption in the IR spectrum is observed at 1769 cm^{-1} for 1, 1764 cm^{-1} for 2 and 1755 cm^{-1} for 3. These values are relatively low for a 4-membered ring ketone which are normally found in the region of 1780 cm^{-1}. This effect points to an interaction between the olefinic bond and the carbonyl group[16]. Through-space conjugation will weaken the carbonyl double bond and consequently it will absorb at a lower wave number.

The UV-spectra of 1 and 2 in MeOH show absorption maxima at λ 197 nm, which may be

Table 2



^{1}H-NMR(400 MHz, $CDCl_3$) and ^{13}C-NMR (100 MHz, $CDCl_3$) data of compounds 1, 2 and 3

proton(s)	chemical shifts		
	1	2	3
a	6.15(137.8)	6.48(143.3)	6.62(145.3)
b	3.16(65.2)	3.08(61.2)	3.16(62.9)
c	3.00(53.6)	2.68(43.9)	2.96(46.9)
d	3.00(43.6)	2.24(35.1)	2.60(44.2)
e	2.83(61.3)	2.32(45.5)	2.52(54.8)
f	1.94(36.9)	1.91(20.0)	2.07(30.8)
		1.85(13.3)	1.91(29.8)
			1.69(25.0)
^{13}C=O	(199.6)	(200.4)	(197.0)

*values within parenthesis are ^{13}C-NMR data

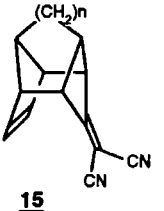
attributed to an isolated carbon-carbon double bond, although this value is considerably higher than that of an isolated olefin without any interaction (λ_{max} in the region of 165-185 nm). Therefore, the UV-spectra of 1 and 2 suggest some interaction between the π-bond systems. Through-space conjugation would give these olefinic bonds in carbonyl brendenes some enone character. Unfortunately, the UV spectrum of 3 could not be measured, because of its insolubility in solvents such as n-hexane and MeOH.

The spectroscopic features of 1, 2 and 3, discussed above, all can be correlated with a shorter distance and an enhanced electronic interaction between the two π-bonds going from 1 to 3. However, fully convincing evidence for the nature of this electronic interaction however, is still lacking. In the following section (2.2.5) further support will be given for their orbital-orbital interaction of non-bonding origin.

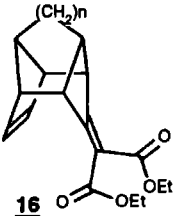
2.2.5 Donor-acceptor type interactions in a brendene-type structure

In the preceding sections (2.2.1-2.2.4) the synthesis of a series of highly strained carbonyl brendenes, *viz.* 1-3, was reported (Scheme 1 and 7). These rigid systems are of particular interest as they possess an enone system in which the carbonyl moiety is positioned orthogonally and in close proximity to the olefinic function. Spectral data strongly suggest that there is considerable electronic interaction between both isolated π-systems.

1 n=1
2 n=2
3 n=3



15



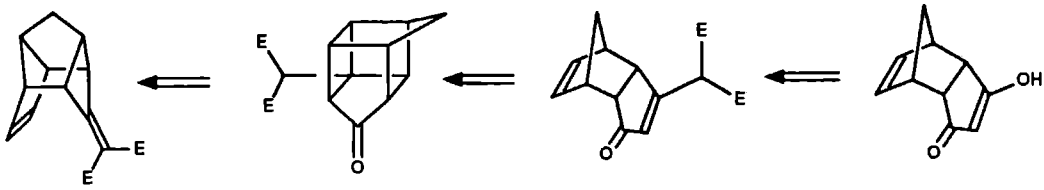
16

An intriguing possibility of demonstrating the existence of orbital-orbital interaction in a cyclic system involves the formation of a potential electrondonor(D) - electronacceptor(A) chromophore, in which the D and A unit are contained in the alicyclic system and separated by sigma bonds. Analysis of the absorption and emission spectra would allow to establish the occurrence of an intramolecular charge-transfer(CT) complex. Such an interaction can be explained by either a through-space interaction(TSI) or a through-bond interaction(TBI)[17].

In order to study this mode of interaction in the present case, the carbonyl group in the carbonyl brendene system 1 must be replaced by another π-system, for example a $>C=C(COOEt)_2$ or $>C=C(CN)_2$ unit as in 15 and 16, which can serve as an acceptor function for the olefinic bond. In this section the first successful synthesis of such a methylene brendene *viz.* 16 (n=1) will be reported and its spectral properties discussed in relation with a possible intramolecular charge-transfer interaction.

The synthesis of methylene brendenes 15 and 16 is conceivable, at least in principle, via a Knoevenagel condensation of the corresponding carbonyl brendene 1 with malononitrile or diethyl malonate, respectively. However, attempted reactions of 1 with malononitrile did not give any condensation product. Starting material was recovered in all cases. The carbonyl reactivity in carbonyl brendene 1 is apparently too low. The alternative strategy follows the same lines as used for the preparation of the carbonyl brendene 1. The retrosynthesis for the methylene brendenes 15 and 16, for n=1, is depicted in Scheme 8. It starts with the readily available tricyclodecadienol 8a, which is actually the Diels-Alder adduct of cyclopentadiene 4a and cyclopentene-1,4-dione 5. Functional group transformations then leads to compound 17, which on photocyclization and subsequent through-cage elimination of 18 should afford the target molecules 15 and 16. Crucial is an effective

Scheme 8



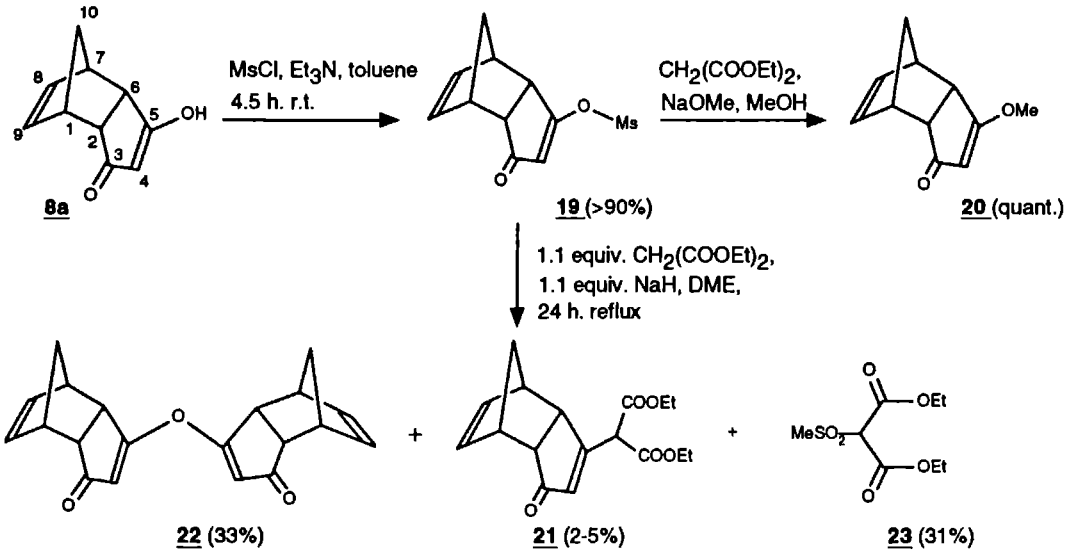
15,**16** (n=1) E= CN, CO_2Et **18** **17** **8a**

preparation of the photoprecursor **17**. An attractive possibility is substitution of the enolic hydroxy group in **8a** by an addition/elimination process. For that purpose this alcohol function needs to be replaced by a better leaving group, *e.g.* a mesyloxy, bromo or chloro group. This concept has been reported for some simpler structures, *e.g.* displacement of chlorine in 3-chloro-cyclohex-2-en-1-one by a malonate unit using sodium hydride in 1,2-dimethoxyethane as the base[18,19] and displacement of a n-butylsulfinyl group in 3-n-butylsulfinyl-cyclohex-2-en-1-one by malonate in THF employing again sodium hydride as the base[19].

Tricyclic enol **8a** was readily converted into mesylate **19** in high yield (>90%) by reaction with methanesulfonyl chloride in toluene in the presence of triethylamine. Treatment of this mesylate with diethyl malonate was first performed using sodium methoxide in methanol as the base[19]. Instead of the desired substitution product **21** quantitative formation of methoxy compound **20** was observed (Scheme 9). Apparently, the reaction with methoxide as the nucleophile proceeds much faster than with malonate. When the malonate anion was produced from diethyl malonate and sodium hydride as the base in 1,2 dimethoxyethane as the solvent[18], only a low yield of desired substitution product **21** was obtained. The major products were "dimeric" ether **22** and sulfone **23**. The malonate anion reacts preferentially at sulfur of mesylate **7** to give sulfone **23**, while the alkoxide of **8a** which is the result of this reaction, now serves as a nucleophile and displaces the mesyloxy group in **19** to produce compound **22**. This anomalous behavior of β-mesyloxy enone **19** (no preccdents of such behavior were found in the literature), may amongst others be attributed to the extremely good leaving ability of the tricyclic enolate anion of **8a**.

The overall pattern of product formation observed for tricyclic mesylate **19** can be accounted for by invoking the HSAB principle[20]. The electrophilic center at C_5 in **19** is relatively hard due to the presence of the mesylate function. Addition of the relatively soft malonate anion at this center will therefore be disfavored. Conversely, addition of the harder methoxide anion, which is highly abundant, will be the preponderant process. In the absence of methoxide or methanol, the addition of malonate at C_5 is apparently again so unfavorable that substitution of the malonate anion at the relatively soft sulfur is now being preferred. This substitution reaction is probably particularly favorable as it leads to the formation of the enolate anion of **8a** which is an excellent leaving group. This relative hard alkoxide anion of **8a** rapidly reacts at the C_5 position in mesylate **19**. The

Scheme 9

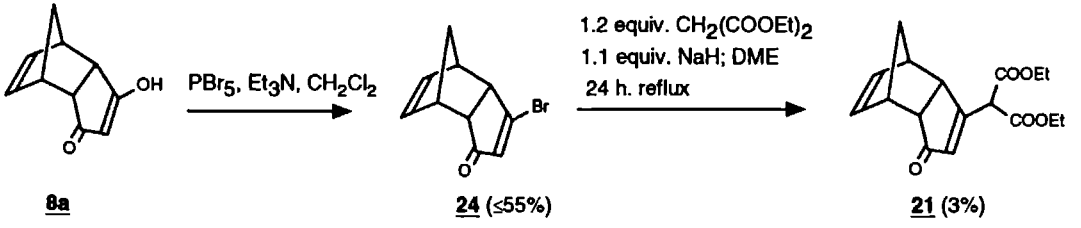


occurrence of about equal amounts of methyl sulfone **23** and enol ether **22** shows that the produced tricyclic enolate anion is immediately consumed by mesylate **19** after its formation. Apparently, steric effects do not play a major role in this product formation as the reaction of the bulky tricyclo enolate of **8a** at C_5 in **19** is not seriously hampered.

The results shown in Scheme 9 clearly indicate that the mesyloxy group is not a suitable leaving group in the addition/elimination reaction with malonate. Based on the above reasoning a halogen substituent at C_5 may have better prospects in this respect.

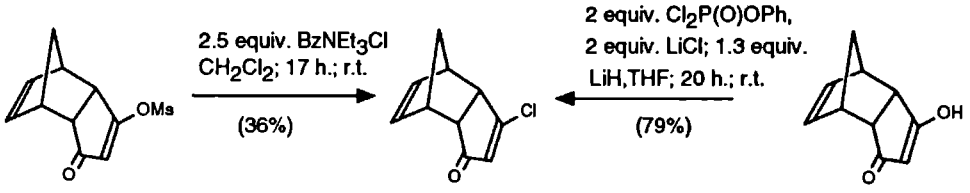
Bromide **24** was prepared from **8a** by treatment with phosphorus pentabromide[21] in 40-55% yield (Scheme 10). Reaction of this enol bromide **24** with sodium malonate, obtained from diethyl

Scheme 10



malonate and sodium hydride, in 1,2-dimethoxyethane gave again a disappointingly low yield of the desired malonate **21**. No attempts were made to analyze this reaction further as both the preparation of the corresponding tricyclic chloride **25** and its conversion into the desired malonate turned out to be much more effective.

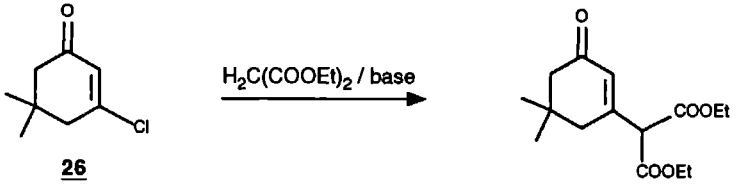
Scheme 11



20 **25** **8a**

For the preparation of chloride **25** as the third precursor for malonate **21**, three methods were considered. Firstly, treatment[18] of **8a** with phosphorus trichloride or phosphorus trichloride/lithium chloride was attempted. These reagents gave very poor yields of **25**. As a second approach displacement of the mesyloxy group in **19** using benzyltrimethylammonium chloride was tried[22].

Scheme 12



26

$H_2C(COOEt)_2$	base	solvent	%
2 equiv.	NaH (2 equiv.)	DME	44 + 41 of s.m.*
2 equiv.	NaH (2 equiv.)	DME, HMPA	72 + 6 of s.m.
2.2 equiv.	LiH (2.2 equiv.)	DME, HMPA	2 + 94 of s.m.
2.2 equiv.	NaH (2.2 equiv.)	DME, HMPA	46 + 46 of s.m.
2.2 equiv.	KH (2.2 equiv.)	DME, HMPA	62 + 27 of s.m.
2.2 equiv.	KOtBu (2.2 equiv.)	DME, HMPA	80 + 6 of s.m.

* s.m. = starting material

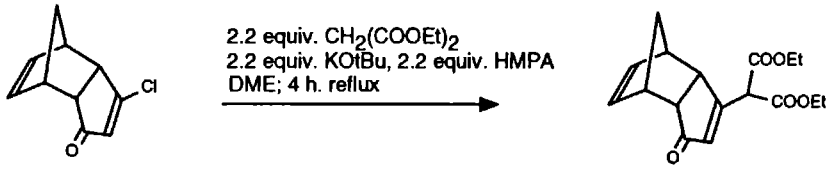
This reaction led to impure **25** in a moderate yield (36%). The third method involves the use of

phenyl dichlorophosphate, lithium hydride and lithium chloride as reported by Liu *et al.*[23] This reaction was successful and the desired chloride **25** was obtained in a yield of 79% (Scheme 11). In this transformation the initial product is an enol phosphate which in the subsequent addition/elimination sequence, is replaced by chlorine.

The conditions for the displacement of chloride in **25** by malonate were first studied for 3-chloro-5,5-dimethyl-cyclohex-2-en-1-one **26** as a model substrate. After some experimentation it was found that hexamethylphosphoramide is essential as co-solvent and that potassium tert-butoxide is the base of choice (Scheme 12).

By applying these optimal conditions for substrate **25** the desired tricyclic malonate **21** was obtained in 86% yield (Scheme 13).

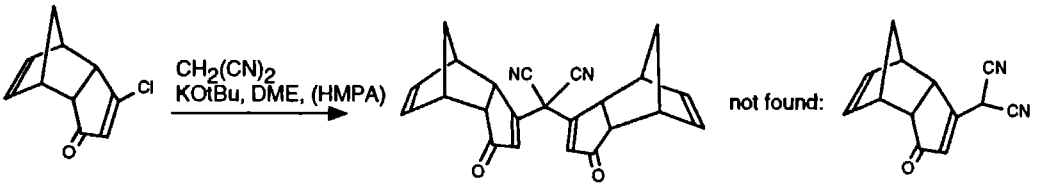
Scheme 13



25 **21** (86%)

Unfortunately, attempts to synthesize the corresponding tricyclic malonodinitril **27** in a similar way by addition of malonodinitril to **25** using a variety of conditions did not meet with succes. In all cases a poorly soluble material was obtained to which on basis of its ^{1}H-NMR spectrum structure **28** was assigned (Scheme 14). Our inability to obtain **27** blocks the route as

Scheme 14



25 **28** **27**

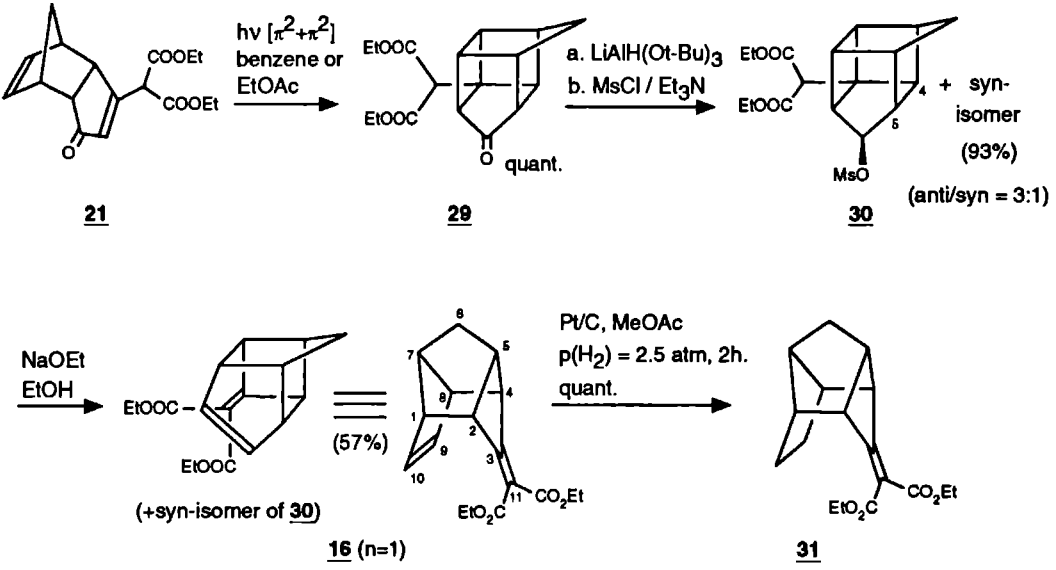
depicted in Scheme 8, to bis(cyano)methylidene compound **15** (n=1).

Tricyclic malonate **21** gave, when subjected to photocyclization in benzene or ethyl acetate, cage compound **29** in a quantitative yield (Scheme 15).

The subsequent step en route to **16** (n=1) is reduction of the carbonyl group in **29** with a suspension of lithium tri-*tert*-butoxyaluminumhydride in ether at -78°C in the same manner as described previously for the reduction of 4-acetoxy-1,3-bishomocubanone (Scheme 5). A mixture of epimeric alcohols was obtained in 95% yield with an *anti*/*syn* ratio of 3:1. Mesylation of this alcohol mixture, performed in the usual way, gave **30** in 93% yield again as a 3:1 mixture of *anti*- en *syn*-isomers.

The Grob through-cage elimination was accomplished with sodium ethoxide in ethanol giving the desired tetracyclic diene **16** (n=1) and unreacted *syn*-mesylate (Scheme 15). Flash chromatography resulted in the isolation of pure **16** (n=1) in a yield of 57% (based on the mixture of *anti*- and *syn*-mesylate).

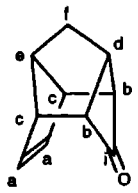
Scheme 15



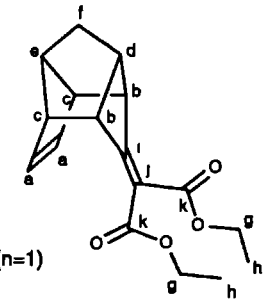
In order to establish any electronic interaction between the olefinic bond and the unsaturated ester moiety in **16** (n=1), it is essential to compare the spectral features of **16** (n=1) with those of derivative **31**, lacking the C_9-C_{10} olefinic bond. The preparation of **31** was readily accomplished by catalytic hydrogenation of **16** (n=1) using platinum on carbon and in methyl acetate as the solvent (Scheme 15). The ^{1}H-NMR spectrum of this hydrogenated product was lacking the olefinic protons at C_9 and C_{10}, while the remainder of the spectrum was in full accord with structure **31**.

The anticipated charge-transfer interaction in compound **16** (n=1) should emerge from its spectra. The ^{1}H- and ^{13}C-NMR data of **16** (n=1) together with those of 2,9-carbonylbrendene **1** are listed in Table 3. Comparison of these spectral data reveals that the olefinic protons *a* in **16** (n=1) are

Table 3 ^{1}H(400MHz;$CDCl_3$)- and ^{13}C(100MHz;$CDCl_3$)-NMR spectral data of 1 and 16 (n=1)



1



16 (n=1)

H/C	δ(^{1}H-NMR,ppm)		δ(^{13}C-NMR,ppm)	
	1	16 (n=1)	1	16 (n=1)
a	6 15	6 01	137 8	135 7
b	3 15	3 44	65 2	50 3
c	3 00	2.98	53 7	53 9
d	3.00	2 98	43.6	48 5
e	2 83	2 98	61 3	62.3
f	1 94	1.73	36 9	35 0
g		4.19		60 2
h		1 28		14 1
i			199.6	96.0
j				114 3
k				173 3
				164 9

found at a somewhat higher field than those in 1. This indicates that the olefinic C_9-C_{10} bond is less electron poor in 16 (n=1) than in 1 suggesting that electron donation of the C_9-C_{10} double bond into the methylene moiety in 16 (n=1) is less pronounced than into the carbonyl function in 1. This is in agreement with the less electrophilic character of the methylene malonic ester unit as compared with the carbonyl function. Although small, this spectral feature again points to significant orbital-orbital interaction between the two orthogonal π-systems.

Another interesting aspect is observed for the bridgehead *b* protons. Since the keto function in 1 is a stronger electron-withdrawing group than the bis(ethoxycarbonyl)methylidene group in 16 (n=1)

(see ^{13}C-values at carbon positions *b* and *i*), a shift to higher field would be expected for the *b* protons of **16** (n=1) compared to those of **1**. However, this is not observed. A possible explanation is a stronger pyramidalization for the protons *b* in **16** (n=1), as the result of the larger distance between the two π-functions due to the steric size of the bis(ethoxycarbonyl)methylidene unit. This fact was substantiated by AM1 calculations, showing an average distance of 2.64 Å between the π-functions of **16** (n=1), which is somewhat larger than that of 2.60 Å found for **1**.

The IR spectrum of **16** (n=1) does not reveal any special effect that would refer to interactions of the π systems.

The UV spectrum of **16** (n=1) shows three absorption maxima, *viz.* at 196, 223 and ca. 255 (shallow shoulder) nm, whereas compound **1** exhibited only one single maximum at 197 nm. The 196 nm band of **16** (n=1) is attributed to the isolated olefinic bond, that at 223 nm to the unsaturated diester moiety and the shoulder at 255 nm to a charge-transfer (CT) interaction. The latter assignment was fully supported by the UV spectrum of compound **31**, which has only one maximum at 227 nm and no detectable absorption maximum at higher wavelength. The observation of a pertinent CT band at 255 nm in **16** (n=1) therefore confirms an electronic interaction between the two orthogonal π systems. It seems likely that this CT band is mainly the result of a through-space interaction, because through-bond interaction in **16** (n=1) would involve at least three σ-bonds in a non-ideal configurational conformation[24].

2.3 Concluding remarks

An effective regiospecific synthesis of three highly strained tetracyclic enones has be accomplished which possess two orthogonal π-systems in close proximity due to the rigidity of the polycyclic skeleton. Spectral data strongly suggest considerable electronic interaction between both isolated π-systems which may significantly effect the chemical reactivity of these 2,9-carbonylbrendenes. The synthesis of a donor-acceptor type brendene was also established. In this molecule the carbonyl oxygen of carbonyl brendene is replaced by a diethoxycarbonylmethylene group. The chemistry of these strained half-cage enones and their derivatives will be discussed in the following chapters.

2.4 Experimental part

General remarks

Melting points were measured on a Reichert Thermopan microscope and are uncorrected. IR spectra were recorded on a Perkin-Elmer 298 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM-390 (90 MHz), a Bruker WH-90 or a Bruker 400 MHz spectrometer with TMS as internal standard. ^{13}C-NMR spectra were measured on a Bruker WP-60 (15.08 MHz, FT) or a Bruker 100 MHz instrument using TMS as an internal standard. For mass spectroscopy a double focussing VG 7070E was used. Capillary GC analyses were performed using a HP 5790 A, containing a cross-linked methyl silicone column. "Flash" chromatography was carried out at a pressure of *ca.* 1.5 bar using silica gel 60H (Merck art.no. 7719) or Merck Aluminium Oxid 150 neutral (Typ T). Thin layer chromatograms (TLC) were run on plastic supported silica gel 60 plates (0.2 mm-layer, F_{254}, Merck art. no. 5735). Solvents were dried using the following methods: tetrahydrofuran was distilled from lithium aluminum hydride just before use. Petroleum ether 60-80 and hexane were distilled from sodium hydride or pure metallic sodium. Diethyl ether was predried over calcium chloride and then distilled from lithium aluminum hydride. Dichloromethane was distilled from calcium chloride. All other solvents used were of analytical grade.

1,3-Cycloheptadiene **4c**

This compound was prepared by reduction of 1,3,5-cycloheptatriene as described by Hafner and Rellensmann[25]. Commercially available 1,3,5-cycloheptatriene (purity ~ 80%) was distilled using a 2m vigreux-column with adjustable distillation-speed (1 drop/20 s), boiling point 116°C (lit[25]: 117°C). Lithium metal (13.9 g, 1.98 mol rinsed with hexane and dried in a N_2-atm.) was dissolved in 1 l. of liquid ammonia at -78°C and (98.8 g, 93% purity, 1 mol) 1,3,5-cycloheptatriene was gradually added. When the addition was complete the color of the reaction mixture had changed to deep red. Then the mixture was allowed to attain r.t. while the ammonia was evaporated. The moist residue was distilled *in vacuo*, yielding 67.6 g (64%) of 1,3-cycloheptadiene, b.p. 116°C, with a purity of 89%. This material was sufficiently pure for the Diels-Alder reaction with cyclopenten-1,4-dione **5**.
^{1}H-NMR ($CDCl_3$; 90MHz) δ: 5.71 (s, 4H, alkene), 2.28 (t, 4H, allylic), 1.82 (m, 2H, methylene) ppm. IR (CCl_4) ν: 3005 (C-H, unsaturated), 2960-2830 (C-H, saturated), 1680-1610 (C=C, diene), 1440-1420 (C-C, alkane) cm^{-1}.

Cyclopenten-1,4-dione **5**

This compound was prepared by oxidation of *cis*-cyclopent-2-en-1,4-diol as described by Rasmussen *et al*[26]. The starting cyclopenten-1,4-diol was synthesized as reported by Kaneko *et al.*[27]

5-Hydroxy-endo-*tricyclo[5.2.1.0^{2,6}]decan-4,8-dien-3-one* **8a**

The Diels-Alder reaction of cyclopentadiene **4a** and cyclopenten-1,4-dione **5** using the procedure of

De Puy and Zaweski[5], gave **8a** in 95% yield.

5-Hydroxy-endo-*tricyclo[5.2.2.0^{2,6}]undecan-3,8-dien-3-one* **8b**

A solution of cyclohexadiene **4b** (3.370 g, 42.1 mmol), cyclopenten-1,4-dione **5** (1.555 g, 16.2 mmol) and five crystals of hydroquinone in a 9:1 mixture of toluene and benzene was placed in a 15 ml. teflon tube, fitted with a screw-threaded metal ring. The capped teflon tube was placed in a high pressure apparatus and subjected to a pressure of 12 kBar for one night. During the reaction the product precipitated. Isolation by filtration and washing with acetone and n-hexane gave 2.468 g (14 mmol; 87%) of **8b**.

^{1}H-NMR (D6-DMSO, 400MHz) δ: 5.95 (dd, 2H, olefine), 4.98 (s, 1H, enol olefine), 2.78 (bs, 2H), 2.52 (dm, 2H), 1.51 (dd, 2H, bridge), 1.23 (dd, 2H, bridge) ppm. EI/MS m/e: 176 (M^+, 47%), 147 (M^+-(C=O)/$C_2H_4^+$-H, 4%), 106 (M^+-$C_3H_2O_2^+$, 8%), 98 ($C_5H_6O_2^+$, 92%), 91 (20%), 80 ($C_6H_8^+$ (cyclohexadiene), 98%), 78 (benzene, 100%). Found: C 74.80, H 6.9 (Calc for $C_{11}H_{12}O_2$: C 74.98, H 6.86).

5-Hydroxy-endo-*tricyclo[5.3.2.0^{2,6}]dodecan-4,11-dien-3-one* **8c**

In the same way as described for **8b** cycloheptadiene **4c** (5.0 g, 47.3 mmol, purity 89%) and cyclopenten-1,4-dione **5** (1.3 g, 13.5 mmol) were subjected to a Diels-Alder reaction at a pressure of 15 kbar. for ca. 20 h. The yield varied between 1.9 and 2.6 g. of a solid material. This product was insoluble in all organic solvents complicating the measurements of spectra.

^{1}H-NMR (D6-DMSO, 90MHz): no sharp signals could be observed due to the presence of polymer material. IR (KBr): no reliable spectrum could be obtained. CI/MS m/e: 191 (M+1, 100%), 121 ((M+1)-(C(O)C=C-OH), 70%), 95 (cycloheptadiene, 30%). The identity of **8c** was proven by its further conversion into the corresponding acetate **6c**.

5-Acetoxy-endo-*tricyclo[5.2.1.0^{2,6}]decan-4,8-dien-3-one* **6a**

A suspension of **8a** (30 g, 0.185 mol) in 150 ml of acetic anhydride, was treated with a catalytic amount of 4-(N,N-dimethylamino)pyridine. Within 30 min. the mixture turned into a clear liquid. After another 5.5 h of stirring the reaction was stopped by removing acetic acid and acetic anhydride in vacuo. The residue was dissolved in chloroform and washed with 0.1N HCl (2×) and aqueous saturated $NaHCO_3$ (2×). Then, the organic layer was dried ($MgSO_4$) and concentrated. After recrystallization from n-hexane 31 g (0.152 mol; 82%) of **6a** was isolated as a white solid, m.p. 87-88.5°C.

IR (KBr) ν: 1780 (C=O, ester), 1685, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$; 90 MHz) δ: 1.6 (q, 2H), 2.2 (s, CH_3CO), 2.8-3.4 (m, 4H), 5.9 (s, 1H), 5.9 (m, 2H) ppm. EI/MS m/e: 204 (M+). Found: C 70.24, H 5.89 (Calc for $C_{12}H_{12}O_3$: C 70.58, H 5.92).

5-Acetoxy-endo-*tricyclo[5.2.2.0^{2,6}]undecan-4,8-dien-3-one* **6b**

To an ice-cold suspension of **8b** (25.4 g, 144.3 mmol) in dichloromethane (125 ml) triethylamine (16 g, 1.1 equiv.) was added. This led, after 10 min. of stirring, to a clear solution. Then acetyl chloride (13.6 g, 1.2 equiv.) was added and the resulting mixture stirred for another 30 min. This resulted in a white precipitate of triethylammonium chloride. Subsequent washing of the reaction mixture with water, aqueous saturated $NaHCO_3$ and again water gave, after drying ($MgSO_4$) and evaporation of the solvent, a darkly yellow-colored oil. Purification of **6b** was performed by dissolving the product in boiling n-hexane, decantation of the hot solution and evaporation of the solvent. This resulted in a lightly yellow-colored oil (24.48 g, 112.3 mmol; 78%), which turned into a solid (m.p.: 57°C) upon standing in the freezer.

IR (CCl_4) ν: 3045 (-CH unsat.), 2980-2860 (-CH sat.), 1790 (-C=O of acetate), 1700 (-C=O of enone), 1600 (-C=C of enone) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400 MHz) δ: 6.18 (s, 1H, AcO-C=C(H)-C=O), 6.10 (t, 1H, -CH=CH-), 5.97 (t, 1H, -CH=CH-), 3.02 (m, 1H), 2.95 (m, 1H), 2.87 (m, 1H), 2.46 (q, 1H), 2.28 (s, 3H, -OC(O)CH_3), 1.61-1.54 (m, 2H, bridge), 1.47-1.31 (m, 2H, bridge) ppm. ^{13}C-NMR ($CDCl_3$; 100 MHz) δ: 208 (quat, -C=O ketone), 180 (quat, -C=O acetate), 166 (quat, AcO-C=C(H)-C=O), 132 (tert, -CH=CH-), 130 (tert, -CH=CH), 119 (tert, AcO-C=C(H)-C=O), 48 (tert), 45 (tert), 33 (tert), 32 (tert), 25 (sec, bridge), 24 (sec, bridge), 21 (prim, -OC(O)CH_3) ppm. EI/MS m/e: 218 (M^+, 16%), 176 (-C(O)CH_2, 67%), 98 (100%), 91 (8%), 80 (95%), 43 ($CH_3C(O)$, 85%). EI/HRMS m/e: 218.0941 (Calc. for $C_{13}H_{14}O_3$ (M^+): 218.0943)

5-Acetoxy-endo-*tricyclo[5.3.2.0^{2,6}]dodecan-4,11-dien-3-one* **6c**

This compound was prepared as described for **6b** using 2.0 g of **8c** in dichloromethane (25 ml), triethylamine (1.15 g, 1.2 equiv.) and acetyl chloride (1.08 g, 1.3 equiv.) in dichloromethane (10 ml.). After the reaction was complete, the mixture was concentrated to about 5 ml and ether (50 ml) was added. The formed precipitate (mostly polymer derived from **4c**) was removed by filtration and the ether solution was washed with water (3x) and aqueous saturated $NaHCO_3$ (1x) solution. The organic layer was dried ($MgSO_4$) and concentrated, to give **6c** as a yellow oil, 400 mg (18%).

IR (CCl_4) ν: 3040 (-CH unsat.), 2960-2860 (-CH sat.), 1790 (-C=O, acetate), 1700 (-C=O of enone), 1600 (-C=C of enone) cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ: 6.24 (s, 1H), 5.89 and 5.86 (dd, 2H, AB), 3.27 (dt, 1H), 2.87 (dd, 1H), 2.72 (m, 2H), 2.28 (s, 3H, OC(O)CH_3), 1.75-1.57 (m, 6H, CH_2) ppm. ^{13}C-NMR (100MHz, $CDCl_3$) δ: 208 (quat, C=CH-C=O), 179 (quat, C=CH-C=O), 166 (quat, C(O)CH_3), 133 and 131 (tert, C=C), 117 (tert, C=CH-C=O), 50 (tert), 47 (tert), 34 (tert), 33 (tert), 28.4 and 28.2 and 23.7 (sec, bridge), 21 (prim, C(O)CH_3) ppm. CI/MS m/e: 233 (M^++1, 35%), 219 (-CH_2, 42%), 205 (-C=O, 7%), 191 (-C(O)CH_3, 100%), 43 ($CH_3C(O)$, 28%)

4-Acetoxypentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-one **7a**

A solution of **6a** (10 g, 49 mmol) in methanol (600 ml) was irradiated for 10 h with a high pressure mercury arc using a Pyrex filter. The course of the reaction was followed by GLC. The solution was

concentrated to give a white crystalline solid, which contained according to the ^{1}H-NMR spectrum 1 equiv. of methanol. This was removed azeotropically *in vacuo* with a 1:1 mixture of chloroform and tetrachloromethane to give **7a** (9.59 g, 47 mmol, 96%) as a dark yellow oil.
IR (KBr) ν: 1770 (C=O), 1740 (C=O, ester) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 90 MHz) δ: 2.2-3.7 (m, 7H), 2.0 (s, 3H, CH_3CO), 1.7 (d, 2H, bridge). EI/MS m/e: 204 (M^+). Found: C 69.48, H 6.31 (Calc. for $C_{12}H_{12}O_3$: C 70.58, H 5.92).

4-Acetoxypentacyclo[5.4.0.0^{2,5}.0^{3,9}.0^{4,8}]undecan-6-one **7b**

A solution of **6b** (11.0 g, 50.5 mmol) in benzene (dried on CaH_2; 600 ml) was irradiated for 40 h with a high pressure mercury arc using a Pyrex filter. The course of the reaction was followed by GLC. The solution was concentrated to give **7b** (10.67 g, 48.9 mmol, 97%) as an orange-yellow oil.
IR (CCl_4) ν: 3000-2860 (-CH sat), 1770-1760 (-C=O of acetate and cyclic ketone) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400 MHz) δ: 3.38 (m, 1H), 2.97 (d, 1H), 2.89 (m, 1H), 2.84 (m, 1H), 2.72 (dd, 1H), 2.46 (dd, 1H), 2.13 (bs, 1H), 2.03 (s, 3H, >COC(O)C$\underline{H}_3$), 1.86 (m, 1H, bridge), 1.49-1.37 (m, 3H, bridge) ppm. ^{13}C-NMR ($CDCl_3$; 100 MHz) δ: 213 (quat, -C=O cyclic ketone), 170 (quat, -C=O acetate), 75 (quat, >C$\underline{O}$C(O)CH_3), 52 (tert), 46 (tert), 45 (tert), 42 (tert), 31 (tert), 30 (tert), 29 (tert), 21 (prim, >COC(O)C$\underline{H}_3$), 19 (sec, bridge), 15 (sec, bridge) ppm. EI/MS m/e: 218 (M^+, 2%), 176 (-C(O)CH_3, 76%), 98 (96%), 91 (22%), 80 (92%), 43 ($CH_3C(O)$, 100%). EI/HRMS m/e: 218.0936 amu (Calc. for $C_{13}H_{14}O_3$: 218.0943)

4-Acetoxypentacyclo[5.5.0.0^{2,5}.0^{3,9}.0^{4,8}]dodecan-6-one **7c**

A solution of **6c** (2.873 g; 12.3 mmol) in benzene (dried on CaH_2; 150 ml) was irradiated for 160 h with a high pressure mercury arc using a Pyrex filter. The course of the reaction was followed by GLC. The solution was concentrated to give **7b** (1.594 g; 6.8 mmol; 55%) as a yellow oil (GLC: 84% pure).
IR (CCl_4) ν: 3000-2860 (-CH sat), 1770-1760 (-C=O of acetate and cyclic ketone) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400 MHz) δ: 3.55 (ddd, 1H), 3.04 (dd, 2H), 2.97 (m, 2H), 2.64 (dd, 1H), 2.25 (dd, 1H), 2.03 (s, 3H, >COC(O)C$\underline{H}_3$), 1.80 (qn, 2H), 1.65-1.45 (m, 4H) ppm. ^{13}C-NMR ($CDCl_3$; 100 MHz) δ: 213 (quat, -C=O cyclic ketone), 170 (quat, -C=O acetate), 74 (quat, >C$\underline{O}$C(O)CH_3), 50.8 (tert), 50.7 (tert), 49.3 (tert), 47.2 (tert), 39.2 (tert), 38.0 (tert), 35.7 (tert), 30.1 (sec, bridge), 28.4 (sec, bridge), 24.6 (sec, bridge), 20.9 (prim, >COC(O)C$\underline{H}_3$) ppm. CI/MS m/e: 233 (M^++1, 12%), 219 (-CH_2, 15%), 205 (-C=O, 10%), 191 (-$CH_3C(O)$, 84%), 190 (-$CH_3C(O)$-H, 100%), 173 (-$CH_3C(O)OH$, 47%), 162 (-$CH_3C(O)$-(C=O), 64%), 145 (-$CH_3C(O)OH$-(C=O), 42%). EI/HRMS m/e: 232.1101 (Calc. for $C_{14}H_{16}O_3$: 232.1099)

4-Acetoxypentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-ols **9a,10a**

A solution of **7a** (16.5 g, 80.9 mmol) in ether (30 ml) was added to a suspension of freshly prepared lithium tri-*tert*-butoxyaluminumhydride (2.1 equiv.) in ether (250 ml) at -78°C. After stirring for 30

min, the mixture was allowed to attain room temperature. Then HCl aq (3%) was added until a neutral water layer was obtained. The ether phase was washed with water, dried ($MgSO_4$) and concentrated, to give **9a** and **10a** (15.34 g, 74.5 mmol, 93%) in a ratio of 5:1 as a colorless oil.
IR (KBr) v: 3400 (OH), 1740 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 90 MHz) δ: 4.4 (s, 0.83H, -CHOH of **9a**), 4.15 (s, 0.17H,-CHOH of **10a**), 3.6 (s, 1H, OH), 2.1-3.3 (m, 7H, cage protons), 2.0 (s, 3H, CH_3COO), 1.6 (ABq, 2H, bridge) ppm. EI/MS m/e: 206 (M^+)

4-Acetoxypentacyclo[5.4.0.0^{2,5}.0^{3,9}.0^{4,8}]undecan-6-ol **9b**

A solution of **7b** (21.7 g, 99.5 mmol) in ether (25 ml) was added to a suspension of freshly prepared lithium tri-*tert*-butoxyaluminumhydride (3.2 equiv.) in ether (300 ml) at 0°C. After stirring for 30 min. the mixture was allowed to attain room temperature. Then HCl aq (10%) was added until a neutral water layer was obtained. The ether phase was washed with water, dried ($MgSO_4$) and concentrated to give **9b** (19.26 g, 87.5 mmol, 88%) as a slightly yellow-colored oil (purity >99%, GLC).
IR (CCl_4) v: 3600-3100 (-OH broad), 3000-2860 (-CH sat), 1740 (-C=O of acetate) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400 MHz) δ: 4.30 (s, 1H, >C(H)OH), 3.11 (d, 1H), 2.99 (dt, 2H), 2.56 (m, 3H), 2.35 (bs, 1H), 2.34 (bs, 1H), 2.02 (s, 3H, -OC(O)CH_3), 1.74 (m, 1H, bridge), 1.58 (m, 1H, bridge), 1.38-1.31 (m, 2H, bridge) ppm. ^{13}C-NMR ($CDCl_3$; 100 MHz) δ: 170 (quat, -C=O), 80 (quat, >COC(O)CH_3), 79 (tert, >C(H)OH), 54 (tert), 45 (tert), 44 (tert), 42 (tert), 31 (tert), 30 (tert), 29 (tert), 21 (prim, >COC(O)CH_3), 18 (sec, bridge), 16 (sec, bridge) ppm. EI/MS m/e: 220 (M^+, 1%), 219 (-H, 5%), 178 (24%), 160 (-OC(O)CH_3-H or -C(O)CH_3-OH, 42%), 108 (54%), 98 (100%), 91 (17%), 80 (83%), 43 ($CH_3C(O)$, 67%). CI/HRMS m/e: 219.1021 (Calc. for $C_{13}H_{17}O_3$ (M^++1): 219.1021).

4-Acetoxypentacyclo[5.5.0.0^{2,5}.0^{3,9}.0^{4,8}]dodecan-6-ol **9c**

A solution of **7c** (1.594 g, 5.8 mmol, 84% pure) in ether (25 ml) was added to a suspension of freshly prepared lithium tri-*tert*-butoxyaluminumhydride (3 equiv.) in ether (25 ml) at -78°C. After stirring for 3 h the mixture was allowed to attain room temperature and was quenched with ether (50 ml). Subsequently diluted HCl aq (3%) was added until a neutral water layer was obtained. The ether phase was washed with water, dried ($MgSO_4$) and concentrated, to give **9c** (972 mg, 4.15 mmol, 62%) as a yellow oil (GLC: 86% pure).
IR (CCl_4) v: 3590-3100 (-OH, broad), 3000-2850 (-CH, sat.), 1735 (-C=O of acetate), 1280-1190 (-C-O- of alcohol/ester) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 90 MHz) δ: 4.24 (s, 1H, -OH), 3.3-3.05 (m, 3H), 2.90-2.40 (m, 5H), 2.0 (s, 3H, -OC(O)CH_3), 1.95-1.45 (m, 6H) ppm. ^{13}C-NMR ($CDCl_3$; 100 MHz) δ: 170 (quat, -C=O of acetate), 89 (quat, >COC(O)CH_3), 78 (quat, -C(H)OH), 52 (tert), 49.5 (tert), 48.7 (tert), 47.2 (tert), 37.3 (tert), 35.8 (tert), 33.6 (tert), 28.7 (sec, bridge), 25.5 (sec, bridge), 25.5 (sec, bridge), 21.4 (prim, -OC(O)CH_3) ppm. CI/MS m/e: 235 (M^++1, 2%), 233 (-2H, 7%), 217 (-OH-H, 8%), 192 (-$CH_3C(O)$-H, 58%), 175 (-OH-$CH_3C(O)$, 100%), 174 (-OH-$CH_3C(O)$-H, 87%). EI/HRMS m/e: $C_{14}H_{18}O_3$-C_2H_3O(acyl) = $C_{12}H_{15}O_2$, 192.1151 (Calc. for $C_{12}H_{15}O_2$: 192.1150 amu)

4-Acetoxy-6-(methylsulphonyloxy)pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane **11a, 12a**

Triethylamine (8.91 g, 88.2 mmol, 1.2 equiv.) was added to an ice-cold solution of an epimeric mixture **9a** and **10a** (15.15 g, 73.5 mmol) and methanesulfonyl chloride (9.26 g, 80.9 mmol, 1.1 equiv.) in toluene (125 ml). The reaction mixture was allowed to attain room temperature and stirred for 30 min. After filtration, the solvent was removed and the residue extracted with ether. The ether phase was washed with diluted HCl aq (3%), aqueous saturated $NaHCO_3$ and water. After drying ($MgSO_4$) and evaporation of the solvent a 5:1 mixture of the epimeric mesylates **11a** and **12a** (18.16 g, 63.9 mmol, 87%) was obtained as an oil which slowly solidified at -20°C.

IR (KBr) v: 1740 (C=O), 1360, 1170 (OSO_2) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 90 MHz) δ: 5.2 (s, 0.83H, -C<u>H</u>OSO_2CH_3 in **11a**), 4.95 (s, 0.17H, -C<u>H</u>OSO_2CH_3 in **12a**), 2.4-3.3 (m, 7H, cage protons), 3.0 (s, 2.5H, C<u>H</u>$_3SO_2O$- in **11a**), 2.95 (s, 0.5H, C<u>H</u>$_3SO_2O$- in **12a**), 2.0 (s, 3H, C<u>H</u>$_3$COO-), 1.6 (ABq, 2H, bridge) ppm. Fractional recrystallization of the epimeric mixture of **11a** and **12a** from methanol gave **11a** analytically pure, m.p. 92-93°C. Found: C 54.92, H 5.65 (Calc. for $C_{13}H_{16}O_5S$: C 54.92, H 5.67).

4-Acetoxy-6-(methylsulphonyloxy)pentacyclo[5.4.0.0^{2,5}.0^{3,9}.0^{4,8}]undecane **11b**

Triethylamine (10.45 g, 103.5 mmol, 1.34 equiv.) was added to an ice-cold solution of alcohol **9b** (17.0 g, 77.3 mmol) and methanesulfonyl chloride (9.77 g, 85.3 mmol, 1.1 equiv.) in ether (150 ml). The reaction mixture was allowed to attain room temperature and stirred for 30 min. After filtration, the ether phase was washed with diluted HCl aq (3%), aqueous saturated $NaHCO_3$ and water. After drying ($MgSO_4$) and evaporation of the solvent **11b** (19.35 g,64.9 mmol,84%) was obtained as a yellow oil.

IR (CCl_4) v: 3000-2860 (-CH sat.), 1735 (-C=O of acetate), 1370 and 1350 (-OSO_2-) cm-1. ^{1}H-NMR ($CDCl_3$; 400 MHz) δ: 5.09 (s, 1H, >C(<u>H</u>)OMs), 3.38 (d, 1H), 3.02 (m, 1H), 3.01 (s, 3H, >C(H)OSO$_2$<u>Me</u>), 2.69 (m, 1H), 2.64 (m, 3H), 2.38 (bs, 1H), 2.03 (s, 3H, -OC(O)<u>Me</u>), 1.78 (m, 1H, bridge), 1.60 (m, 1H, bridge), 1.35-1.39 (m, 2H, bridge) ppm. ^{13}C-NMR ($CDCl_3$; 100 MHz) δ: 170 (quat, -C=O of acetate), 86 (tert, >C(H)OMs), 78 (quat, -<u>C</u>OAc), 53 (tert), 44 (tert), 42 (tert), 38 (tert), 31 (tert), 30 (tert), 29 (tert), 21 (prim, -<u>C</u>H$_3$ of acetate), 18 (sec, bridge), 16 (sec, bridge) ppm. EI/MS m/e: 298 (M^+, 0.5%), 254 (M^+-$CH_3C(O)$-H, 9%), 239 (M^+-$CH_3C(O)O$, 5%), 219 (M^+-CH_3SO_2, 14%), 177 (M^+-$CH_3C(O)$-CH_3SO_2, 29%), 160 (M^+-$CH_3C(O)O$-$CH_3S(O)_2O$, 29%), 97 (17%), 91 (23%), 80 (CH_3SO_2H, 100%), 43 (35%). EI/HRMS m/e: (M-CH_3CO_2(acyl)) 239.0734 (Calc. for ($C_{14}H_{18}O_5S$ - $C_2H_3O_2$ = $C_{12}H_{15}O_3S$): 239.0742)

4-Acetoxy-6-(methylsulphonyloxy)pentacyclo[5.5.0.0^{2,5}.0^{3,9}.0^{4,8}]dodecane **11c**

A mixture of triethylamine (469 mg, 4.6 mmol, 1.3 equiv.) and toluene (10 ml) was added to a solution of alcohol **9c** (972 mg, 3.6 mmol, 86% pure) and methanesulfonyl chloride (560 mg, 4.3 mmol, 1.2 equiv.) in toluene (30 ml). The reaction mixture was stirred for 30 min. during which

triethylammonium chloride precipitated. After filtration, the residue was washed with hexane and the filtrate concentrated *in vacuo*. Then, the crude product was dissolved in ether (25 ml) and washed with HCl aq (3%)(2x), and aqueous saturated $NaHCO_3$ and water. After drying ($MgSO_4$) and evaporation of the solvent **11c** (1.094 g, 2.845 mmol, 79%) was obtained as a yellow oil (GLC: 80% pure).

IR (CCl_4) ν: 3020-2820 (-CH sat.), 1735 (-C=O of acetate), 1390-1330, 1270-1200, 1175 cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400 MHz) δ: 5.00 (s, 1H), 3.32 (d, 1H), 3.18 (ddd, 1H), 3.00 (s, 3H, Me), 2.85-2.65 (m, 4H), 2.55 (q, 1H), 2.03 (s, 3H, Me), 1.81 (qn, 2H), 1.65-1.40 (m, 4H) ppm. ^{13}C-NMR ($CDCl_3$; 100 MHz) δ: 170, 137, 84, 50, 48.6, 47.3, 38.0, 37.3, 36.3, 33.6, 28.5, 28.1, 24.9, 21.2 ppm. CI/MS m/e: 313 (M^++1, 0.2%), 311 (-H_2, 0.2%), 253 (-H_2-$OC(O)CH_3$, 12%), 249 (2%), 217 (-$CH_3S(O)_2OH$, 26%), 175 (-$C(O)CH_3$-$OS(O)_2CH_3$, 100%), 146 (11%), 131 (7%), 91 (10%)

Tetracyclo[5.3.0.0^{2,5}.0^{4,8}]dec-9-en-3-one **1**

A solution of epimeric mesylates **11a** and **12a** (ratio 1:5) (18.0 g, 63.4 mmol) in methanol was added dropwise to a solution of sodium methoxide (3.35 g, 145.7 mmol, 2.3 equiv. Na) in methanol (250 ml). After stirring at room temperature for 30 min., methanol was removed *in vacuo* at room temperature until a concentrated turbid oil was obtained. This residue was dissolved in ether and the ether phase washed with HCl aq (3%). The water phase was extracted with ether, and the combined ether layers dried ($MgSO_4$) and concentrated, to give a yellow oil. Flash column chromatography (silica 60H, hexane/ethyl acetate (5:1)) gave carbonyl brendene **1** (7.5 g, 51.4 mmol, 81%) as an oil which slowly solidified on standing. Recrystallization from hexane gave an analytically pure sample, m.p. 129-130°C.

IR (CCl_4) ν: 1765 (C=O), 1330, 1075 cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400 MHz) δ: 6.15 (s, 2H, H_a), 3.16 (dt, 2H, H_b), 3.00 (m, 2H, H_c), 3.00 (m, 1H, H_d), 2.83 (se, 1H, H_e), 1.94 (bs, 2H, H_f) ppm. ^{13}C-NMR ($CDCl_3$; 100 MHz) δ: 199.6 (quat, 1C, -C=O), 137.8 (tert, 2C, C_a), 65.2 (tert, 1C, C_b), 61.3 (tert, 1C, C_e), 53.6 (tert, 2C, C_c), 43.6 (tert, 1C, C_d), 36.9 (sec, 1C, C_f) ppm. EI/MS m/e: 146 (M^+, 45%), 117 (-(C=O)-H, 100%), 104 (-(C=O)-CH_2, 90%), 91 (54%). EI/HRMS m/e: 146.0725 (Calc. for $C_{10}H_{10}O$: 146.0732). Found: C 54.88, H 5.69 (Calc. for $C_{10}H_{10}O$: C 54.92, H 5.67)

Tetracyclo[5.4.0.0^{3,11}.0^{4,8}]undec-5-en-2-one **2**

A solution of mesylate **11b** (20 g, 67.1 mmol) in methanol (25 ml) was gradually added to an ice-cold solution of sodium methoxide (3.57 g, 155.2 mmol, 2.3 equiv. Na) in methanol (225 ml). After stirring at room temperature for 30 min., methanol was removed *in vacuo* at room temperature until a concentrated turbid oil was obtained. This residue was dissolved in ether and the ether phase washed with HCl aq (3%). The water phase was extracted with ether and the combined ether layers dried ($MgSO_4$) and concentrated to give a yellow colored solid. Flash column chromatography (silica 60H, hexane/ethyl acetate (4:1)) gave carbonyl brendene **2** (8.3 g, 51.9 mmol, 77%) as white needle-shaped crystals, m.p. 99°C.

IR (CCl_4) v: 3073 (-CH unsat.), 3000-2860 (-CH sat.), 1764 (-C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400 MHz) δ: 6.48 (dd, 2H, H_a), 3.08 (dt, 2H, H_b), 2.68 (m, 2H, H_c), 2.32 (tt, 1H, H_e), 2.24 (tt, 1H, H_d), 1.91 (m, 2H, H_f), 1.85 (m, 2H, H_f) ppm. ^{13}C-NMR ($CDCl_3$; 100 MHz) δ: 200.4 (quat, 1C, -C=O), 143.3 (tert, 2C, C_a), 61.2 (tert, 1C, C_b), 45.5 (tert, 1C, C_e), 43.9 (tert, 2C, C_c), 35.1 (tert, 1C, C_d), 20.0 (sec, 1C, C_f), 13.3 (sec, 1C, C_f) ppm. EI/MS m/e: 160 (M^+, 3%), 131 (-(C=O)-H, 30%), 116 (-C_2H_4-(O)), 100%), 104 (-(C=O)-C_2H_4, 32%), 91 (67%). EI/HRMS m/e: 160.1010 (Calc. for $C_{11}H_{12}O$: 160.1003)

Tetracyclo[5.5.0.0^{3,12}.0^{4,8}]dodec-5-en-2-one **3**

A solution of sodium methoxide (0.156 g, 6.78 at. Na) in methanol (20 ml) was added dropwise to a solution of the mesylate **11c** (1.094 g, 80% pure) in methanol (35 ml). After stirring at room temperature for 3 h, methanol was removed *in vacuo* at room temperature until a concentrated turbid oil was obtained. This residue was dissolved in ether and the ether phase washed with HCl aq (3%). The water phase was extracted with ether (2x), and the combined ether layers dried ($MgSO_4$) and concentrated to give a yellow-colored oil (609 mg). Flash column chromatography (Al_2O_3 neutral 60H, hexane/ethyl acetate (4:1)) gave carbonyl brendene **3** (330 mg, 1.92 mmol, 65%) as a white solid, m.p. 85°C.

IR (CCl_4) v: 3060 (-CH unsat.), 3000-2860 (-CH sat.), 1755 (-C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400 MHz) δ: 6.62 (dd, 2H, H_a), 3.16 (ddd, 2H, H_b), 2.96 (ddd, 2H, H_c), 2.60 (q, 1H, H_d), 2.52 (se, 1H, H_e), 2.07 (q, 2H, H_f), 1.91 (q, 2H, H_f), 1.69 (m, 2H, H_f) ppm. ^{13}C-NMR ($CDCl_3$; 100 MHz) δ: 197.9 (quat, 1C, -C=O), 145.3 (tert, 2C, C_a), 62.9 (tert, 1C, C_b), 54.8 (tert, 1C, C_e), 46.9 (tert, 2C, C_c), 44.2 (tert, 1C, C_d), 30.8 (sec, 1C, C_f), 29.8 (sec, 1C, C_f), 25.0 (sec, 1C, C_f) ppm. CI/MS m/e: 175 (M^++1, 33%), 174 (M^+, 15%), 157 (16%), 146 (-(C=O), 43%), 131 (-C_2H_4-(O), 53%), 117 (-C_2H_4-(C=O), 74%), 91 (100%). EI/HRMS m/e: 174.10445 (Calc. for $C_{11}H_{12}O$: 174.10447).

Attempted reaction of **1** *with malononitrile*

A solution of **1** (146 mg, 1 mmol) and malononitrile (75 mg, 1.10 mmol) in benzene (5 ml) with piperidine (3 drops) as a catalyst, was heated at reflux for 24 h. After this time no product formation had take place (GLC).

The same reaction with 150 mg (2.21 mmol), 300 mg (4.41 mmol) and 600 mg (8.82 mmol) of malononitrile without a solvent also did not result in a reaction.

5-Methylsulphonyloxytricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one **19**

Et_3N (3.83 g, 37.8 mmol, 1.2 equiv.) was added to a suspension of **8a** (5.10 g, 31.5 mmol) in toluene (50 ml), followed by methanesulfonyl chloride (3.61 g, 31.5 mmol). The reaction mixture was stirred for 4.5 h. The white precipitate formed was removed by filtration. The filtrate was extracted with water and aqueous saturated $NaHCO_3$. Then, the organic phase was dried ($MgSO_4$) and concentrated *in vacuo*, to give **19** (7.3 g, 30.4 mmol, 97%) as a yellow-orange oil, which crystallized at r.t. on

standing. Recrystallization from toluene gave **19** as white crystals, purity >99% (cap. GC), m.p. 72-73°C.

IR (CCl_4) v: 3060 (-CH unsat.), 3000-2860 (-CH sat.), 1710 (C=O), 1600 (C=C,enone), 1390 + 1375 + 1200 (-OSO_2-) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 90MHz) δ: 6.10 + 5.95 (AB-coupling, both dd, 2H, H_8+H_9), 5.75 (s, 1H, H_4), 3.40 (pseudo t, 1H, H_6), 3.25-2.85 (m, 3H, H_1+H_2+H_7), 3.25 (s, 3H, -CH_3), 1.80 + 1.60 (AB-coupling, both d, 2H, H_{10}) ppm. CI/MS m/e: 241 (M^++1, 100%), 213 (-C=O, 53%), 203 (42%), 175 (-cyclopentadiene, 86%), 161 (-H^+, -SO_2CH_3, 59%), 66 (cyclopentadiene, 67%). EI/HRMS m/e: 240.0502 (Calc. for $C_{11}H_{12}O_4S$: 240.0456)

5-Methoxy-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one **20**

After sodium (200 mg, 8.7 m.at.) was dissolved in ice-cooled MeOH (7 ml) under nitrogen, diethyl malonate (145 mg, 0.91 mmol) was added and the mixture stirred for 15 min. Then, a solution of **19** (197 mg, 0.82 mmol) in MeOH (15 ml) was added. The reaction mixture was heated under reflux for 17 h and then quenched with aqueous saturated NH_4Cl (50 ml) and extracted with ether. The organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*, to give **20** (141 mg, 0.80 mmol, 98%) as a clear oil, which crystallized on standing, m.p. 74-75.5 °C (toluene)[9].

^{1}H-NMR ($CDCl_3$; 90MHz) δ: 6.00 + 5.80 (AB-coupling, both dd, 2H, H_8+H_9), 5.05 (s, 1H, H_4), 3.70 (s, 3H, -OCH_3), 3.25-2.80 (m, 4H, H_1+H_2+H_6+H_7), 1.75 + 1.50 (AB-coupling, both d, 2H, H_{10}) ppm.

Reaction of **19** *with diethyl malonate and NaH in DME*

A solution of diethyl malonate (355 mg, 2.22 mmol) in DME (15 ml) was gradually added to a stirred suspension of NaH (55 mg, 2.29 mmol) in DME (15 ml) under nitrogen. After the reaction mixture was heated at reflux for 30 min. a solution of **19** (481 mg, 2.00 mmol) in DME (25 ml) was gradually added to the still warm solution. After heating at reflux for another 24 h the reaction mixture was cooled to 0°C and quenched with ice water (200 ml). The resulting aqueous mixture was extracted with ether, the organic fraction dried ($MgSO_4$) and concentrated *in vacuo*, to give **22** (200 mg, 33%) as a white solid, m.p. 155-157°C.

The water fraction was carefully acidified with concentrated HCl to pH = 1 and extracted with ether. The ether extract was dried ($MgSO_4$) and concentrated *in vacuo*, to give **23** (150 mg, 0.6 mmol, 31%) as a colorless oil.

Compound **23** was obtained independently from sodium diethyl malonate in DME (20 ml), prepared as described above from (297 mg, 1.9 mmol) of diethyl malonate and NaH (46 mg, 1.9 mmol), upon treatment with methanesulfonyl chloride (230 mg, 2.0 mmol) following the above procedure by replacing **19** by methanesulfonyl chloride.

Di-[5-(tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one)-yl]-ether **22**:

IR (CCl_4) v: 3060 (-CH unsat.), 3000-2860 (-CH sat.), 1710 (-C=O), 1615 (C=C of enone), 1580 (C=C of enone) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 90MHz) δ: 6.10+5.90 (AB-coupling, both dd, 2H, $H_{8/8'}$+$H_{9/9'}$), 5.50 (s, 1H, $H_{4/4'}$), 3.05-2.90 (m, 4H, $H_{1/1'}$+$H_{2/2'}$+$H_{6/6'}$+$H_{7/7'}$), 1.85 + 1.60

(AB-coupling, both d, 2H, $H_{10/10'}$) ppm. CI/MS m/e: 307 (M^++1, 100%), 279 (-(C=O), 14%), 241 (-cyclopentadien, 21%), 233 (74%), 175 (-2 × cyclopentadiene, 74%), 137 (91%), 97 (94%), 67 (cyclopentadiene+1, 25%). EI/HRMS m/e: 306.1246 (Calc. for $C_{20}H_{18}O$: 306.1256).

Diethyl 2-methylsulphonyl-malonate **23**:

IR (CCl_4) ν: 3000-2860 (-CH sat.), 1760-1730 (-C=O), 1345-1330 (-SO_2-), 1120 (-SO_2-) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 90MHz) δ: 4.80 (s, 1H, -C**H**$(COOEt)_2$), 4.35 (q, 4H, -C$H_2$$CH_3$), 3.25 (s, 1H, -$SO_2CH_3$), 1.30 (t, 6H, -$CH_2CH_3$) ppm. CI/MS m/e: 239 ($M^+$+1, 100%), 211 (-(C=O), 40%), 193 (-H^+, -OEt, 57%), 167 (98%)

5-Bromotricyclo[5.2.1.0^{2,6}]-deca-4,8-dien-3-one **24**

Et_3N (585 mg, 5.79 mmol) was added to a suspension of **8a** (314 mg, 1.94 mmol) in CH_2Cl_2 (30 ml). To the clear solution thus obtained, a solution of PBr_5 (914 mg, 2.19 mmol) in CH_2Cl_2(30 ml) was gradually added and the reaction mixture stirred for 100 h at r.t. After extraction with successively water (30 ml), aqueous saturated $NaHCO_3$ (30 ml), HCl aq (3%) (30 ml) and water (30 ml), the organic fraction was dried ($MgSO_4$) and concentrated *in vacuo*, to give a dark brown oil (330 mg), which was dissolved in CCl_4. After several hours a black material precipitated, which was removed by filtration. The filtrate was concentrated *in vacuo*, to give **24** (236 mg, 1.05 mmol, 54%) as a brown oil, which crystallized on standing at -18°C as beige-brown crystals but melted again at r.t., purity 93% (cap. GC).

IR (CCl_4) ν: 3060 (-CH unsat.), 3000-2860 (-CH sat.), 1710 (-C=O), 1575 (-C=C- of enone) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 90MHz) δ: 6.15 (s, 1H, H_4), 6.00 (m, 2H, H_8+H_9), 3.55 (ddd, 1H, H_6), 3.35-3.05 (m, 2H, H_1+H_7), 3.00 (pseudo t, 1H, H_2), 1.80 + 1.60 (AB-coupling, resp. ddd and d, 2H, H_{10}) ppm. CI/MS m/e: 227/225 (M^++1, 85/88%), 189/187 (23/24%), 161/159 (-cyclopentadiene, 12.5/13.0%), 145 (-H^+, -Br, 100%), 66 (cyclopentadiene, 48%).

Reaction of **24** *with diethyl malonate and NaH in DME*

The same procedure as used for the synthesis of **22** and **23** from **19** was followed for the reaction of **24** (86 mg, 0.38 mmol) with diethyl malonate (68 mg, 0.42 mmol) and NaH (11 mg, 0.46 mmol) dissolved in DME (40 ml). After stirring for 24 h at reflux conditions only 2.5% of desired product **21** was detected by cap. GC; the remaining material consisted of **24** and diethyl malonate.

5-Chlorotricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one **25**

Procedure a: Using benzyltriethylammonium chloride as chloride donor.

The procedure described by Kowalski et al.[22] was followed using **19** (1.06 g, 4.42 mmol), benzyltriethylammonium chloride (2.5 g, 11 mmol) and BF_3-etherate (600 μL) in CH_2Cl_2 (15 ml). After stirring for 17 h CH_2Cl_2(80 ml) was added, and the mixture extracted with water (20 ml) and an aqueous saturated NaCl solution (20 ml). The organic fraction was then dried ($MgSO_4$) and concentrated *in vacuo*. For the removal of the ammonium salts the residue (1.3 g) was dissolved in

ether and filtered over some silicagel, to give **25** (290 mg, 1.61 mmol, 36%) as white crystals (GLC: 88% pure). The 10% of **19**, still present in the crude product, was removed by washing the crystals with petrol ether (80-110°C), to give **25** (160 mg, 0.9 mmol, 20%) with a purity of 97%, m.p. 63-65°C.

Procedure b: Using $Cl_2P(O)Ph$ as chloride donor.

The procedure described by Liu, Lamoureux and Llinas-Brunet was followed.[23]

To an ice-cooled suspension of **8a** (4.69 g, 29.0 mmol) in $LiAlH_4$-dried THF (100 ml) and under argon LiCl (2.5 g, 58.8 mmol), LiH (0.3 g, 37.7 mmol) and phenyl dichlorophosphate (9 ml, 60 mmol) were added successively. The resulting solution was stirred for 20 h at r.t. After cooling to 0°C, aqueous saturated $NaHCO_3$ (100 ml) was added, and the mixture extracted with CH_2Cl_2 (4x). The combined extracts were washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (5.6 g), which slowly crystallized. Crude **25** was recrystallized from petrol ether (80-110°C) to give **17c** (4.11 g, 22.8 mmol, 79%) as a white solid, m.p. 66°C.

IR (CCl_4) ν: 3060 (-CH unsat.), 3000-2860 (-CH sat.), 1705 (-C=O), 1585 (-C=C- of enone) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 6.05 + 5.94 (AB-coupling, both dd, J=5.5Hz, J'=3Hz, 2H, H_8+H_9), 5.95 (d, J=1Hz, 1H, H_4), 3.47 (ddd, J=5Hz, J'=4Hz, J"=1Hz, 1H, H_6), 3.23 (m, 1H, $H_{1/7}$), 3.14 (m, 1H, $H_{7/1}$), 3.03 (dd, J=5.5Hz, J'=4.5Hz, 1H, H_2), 1.81 + 1.60 (AB-coupling, resp. ddd (J=8.5Hz, J'=J"=1.5Hz) and d (J=8.5Hz), 2H, H_{10}) ppm. CI/MS m/e: 181/183 (M^++1, 6.8/2.6%), 145 (-Cl, 2.5%), 67 (cyclopentadiene+H^+, 38%)

These spectral data are in agreement with those reported in ref. 23.

Reaction of 3-chloro-5,5-dimethylcyclohex-2-en-1-one with diethyl malonate

The same procedure as described for the reaction of **19** with diethyl malonate was followed, using 3-chloro-5,5-dimethyl-cyclohex-2-en-1-one **26** (195 mg, 1.23 mmol), diethyl malonate (386 mg, 2.41 mmol), NaH (58 mg, 2.42 mmol) in DME (25 ml). This reaction was also carried out in the presence of HMPA (5 drops)

In a similar manner **26** (2.0 mmol), diethyl malonate (4.4 mmol), HMPA (4.4 mmol) and a base (4.4 mmol) in DME (30 ml) were reacted. The bases used were: LiH, NaH, KH and KOtBu.

The resulting reaction mixtures were analyzed by cap. GC, see for the results scheme 12.

2-(5,5-Dimethyl-3-oxo-cyclohex-1-enyl)malonic acid diethyl ester

^{1}H-NMR ($CDCl_3$; 90MHz) δ: 6.00 (t, 1H, -C**H**=C), 4.25 (m, 5H, -OC**H**$_2$CH$_3$ and -C**H**(COOEt)$_2$), 2.35 (d, 2H, -C**H**$_2$C=C), 2.20 (s, 2H, -C**H**$_2$C=O), 1.25 (t, 6H, -OCH$_2$C**H**$_3$), 1.05 (s, 6H, -C(C**H**$_3$)$_2$) ppm.

2-(5-Oxo-tricyclo[5.2.1.0^{2,6}]deca-3,8-dien-3-yl)-malonic acid diethyl ester **21**

A solution of diethyl malonate (2.97 g, 18.5 mmol) in DME (25 ml) was gradually added to a stirred suspension of KOtBu (2.09 g, 18.6 mmol) in DME (25 ml), under nitrogen. The reaction mixture was stirred for 30 min. while heating under reflux. When still warm a solution of **25** (1.52 g, 8.4

mmol) and HMPA (3.36 g, 18.8 mmol) in DME (25 ml) was gradually added. After stirring, while heating under reflux for 4 h, the reaction mixture was cooled to 0°C and quenched with ice water (250 ml). Careful acidification with concentrated HCl(aq) to pH = 1, was followed by extraction with chloroform. The combined chloroform extracts were dried ($MgSO_4$) and concentrated *in vacuo*, to give a clear yellow oil, which contained a considerable amount of diethyl malonate and HMPA. Flash chromatography (silica gel; n-hexane/EtOAc=3/1), gave **21** (2.20 g, 7.2 mmol, 86%) as a pale yellow oil, with a purity of 97%(cap. GC).

IR (CCl_4) ν: 3060 (-CH unsat.), 3000-2860 (-CH sat.), 1740-1730 (-C=O of ester), 1710-1700 (-C=O of enone), 1610 (-C=C- of enone) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 6.03 (s, 1H, H_4), 6.00 + 5.75 (AB coupling, both dd, J=5.5Hz, J'=3Hz, 2H, H_8+H_9), 4.26 (s, 1H, -C<u>H</u>$(COOEt)_2$), 4.25 (q, 4H, -OC<u>H_2</u>CH_3), 3.55 (dd, J=5Hz, J'=4Hz, 1H, H_6), 3.21 (m, 1H, $H_{1/7}$), 3.00 (m, 1H, $H_{7/1}$), 2.94 (dd, J=J'=5Hz, 1H, H_2), 1.77 + 1.61 (AB-coupling, resp. ddd (J=8.5Hz, J'=1.5Hz, J"=1Hz) and d (J=8.5Hz), 2H, H_{10}) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 208.7 (quat, C=CH-<u>C</u>=O), 169.0 (quat, <u>C</u>=CH-C=O), 165.9 + 165.7 (quat, <u>C</u>=O of ester functions), 135.8 (tert, C=<u>C</u>H-C=O), 133.7 +131.8 (tert, <u>C</u>=<u>C</u> of isolated olefin), 62.3 + 62.2 (sec C 2X <u>C</u>H_2 of ester unit) 54.7 (-<u>C</u>H$(COOEt)_2$), 52.3 (sec, bridge), 51.6 (tert), 49.7 (tert), 44.3 (tert), 43.7 (tert), 13.9 (-<u>C</u>H_3 of ester unit) ppm. <u>CI/MS</u> m/e: 305 (M^++1, 86%), 277 (-(C=O), 23%), 267 (32%), 259 (-H^+, -OEt, 31%), 239 (-cyclopentadiene, 13%), 231 (-H^+, -(COOEt), 24%), 66 (cyclopentadiene, 25%). <u>EI/HRMS</u> m/e: 304.1299 (Calc. for $C_{17}H_{20}O_5$: 304.1311).

<u>4-[Bis(ethoxycarbonyl)methyl]-pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]deca-6-one</u> **<u>29</u>**

A solution of **<u>21</u>** (200 mg, 0.66 mmol) in 2.5 ml dried benzene was irradiated for 16-20 h in a NMR-tube using a high-pressure mercury arc with a Pyrex filter. After evaporation of the solvent, **<u>29</u>** (197 mg, 0.65 mmol, 99%) was obtained as a yellow oil, which was sufficiently pure for further use. Irradiation in EtOAc gave an identical result.

<u>IR</u> (CCl_4) ν: 2990 (-CH sat.), 1750 (-C=O ester), 1735 (-C=O ketone) cm^{-1}. <u>^{1}H-NMR</u> ($CDCl_3$; 400MHz) δ: 4.19 (q, 4H, -OC<u>H_2</u>CH_3), 3.58 (s, 1H, -C<u>H</u>$(COOEt)_2$), 3.08 (m, 3H, cage protons), 2.92 (m, 2H, cage protons), 2.49 (d, 1H, cage proton), 2.33 (m, 1H, cage protons), 1.74 + 1.60 (AB-system, both dd, J=11Hz, 2H, bridge protons), 1.26 (t, 6H, -OCH_2C<u>H_3</u>) ppm. <u>^{13}C-NMR</u> ($CDCl_3$; 100MHz) δ: 215 (quat, <u>C</u>=O of ketone), 167.2 (quat, 2C, <u>C</u>=O of ester), 61.4 (sec C 2X -<u>C</u>H_2 of ester unit), 54.3 (tert, <u>C</u>H of diethyl malonate function), 51.1 (tert), 44.9 (tert), 44.4 (tert), 43.9 (tert), 42.8 (tert), 41.9 (quat), 41.4 (tert), 41.2 (sec, bridge), 36.1 (tert), 14.0 (-<u>C</u>H_3 of ester unit) ppm. <u>CI/MS</u> m/e: 305 (M^++1, 41%), 277 ((M^++1)-(C=O), 12%), 259 ((M^++1)-(-OEt), 100%), 231 (M^+-(-COOEt), 34%), 213 (21%). <u>EI/HRMS</u> m/e: 304.1296 (Calc. for $C_{17}H_{20}O_5$: 304.1311).

<u>4-[Bis(ethoxycarbonyl)methyl]-6-methylsulphonyloxy-pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane</u> **<u>30</u>**

A solution of **<u>29</u>** (1.83 g, 6.02 mmol) in dry ether (10 ml) was slowly added to a cooled (-78°C) freshly prepared suspension of $LiAlH(OtBu)_3$ [slow addition of tBuOH (1.49 g, 20.14 mmol) in dry

ether (20 ml) to a suspension of $LiAlH_4$ (247 mg, 6.5 mmol) in dry ether (20 ml), followed by stirring for 0.5 h]. The reaction mixture was allowed to attain r.t. and was then neutralized with HCl aq (3%). The ethereal layer was washed with water, dried ($MgSO_4$) and concentrated, to give a light yellow oil (1.760 g, 5.75 mmol, 96%) consisting of diastereomeric alcohols (ratio ≈ 3:1).

IR (CCl_4) ν: 3300 (-OH), 3000-2820 (-CH sat.), 1720 (-C=O of ketone in cage) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 4.21 (m, 5H, $-CO_2CH_2CH_3$ + $-CH(COOEt)_2$), 3.0 (bs, 1H), 2.8 (m, 2H), 2.75 (m, 1H), 2.65 (m, 2H), 2.55 (m, 1H), 2.46 (m, 1H), 2.32 (bs, 1H), 1.62 + 1.47 (AB-system, both d, 2H, bridge protons), 1.28 (m, 6H, $-CO_2CH_2CH_3$) ppm. EI/MS m/e: 307 (M^++1, 100%), 289 ($-H_2O$, 68%), 233 (12%), 215 (31%), 187 (14%), 167 (20%), 146 (13%), 129 (19%). EI/HRMS m/e: 306.1466 (Calc. for $C_{17}H_{22}O_5$: 306.1467).

To this mixture of diastereomeric alcohols (1.669 g, 5.45 mmol), dissolved in toluene (25 ml), was added Et_3N (570 mg, 5.64 mmol) followed with mesyl chloride (641 mg, 5.6 mmol) at 0°C. Stirring was continued for 4.5 h The precipitated Et_3N•HCl was removed by filtration and the filtrate was extracted with water and HCl aq (3%), dried ($MgSO_4$) and concentrated *in vacuo*, to give **30** (1.939 g, 5.05 mmol, 93%) as a yellow oil (GLC: 92% pure). Flash chromatography (silicagel; n-hexane/EtOAc=2/1) gave **30** as a mixture of diastereomers, ratio 3:1 (In another experiment 5:1, the temperature control during the reduction is essential), purity 97%.

IR (CCl_4) ν: 3000-2820 (-CH sat.), 1720 (-C=O of ketone in cage) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 5.98 + 5.01 (2×s, 1H, -CHOMs), 4.21 (m, 5H, $-CO_2CH_2CH_3$ + $-CH(COOEt)_2$), 3.04 (bs, 1H), 3.01 + 2.97 (2×s, 3H, $-OSO_2CH_3$), 2.95 (m, 1H), 2.86 (m, 1H), 2.77 (m, 1H), 2.71 (q, 1H), 2.66 (m, 1H), 1.70 (s, 1H), 1.67 + 1.50 (AB-system, both d, 2H, bridge protons), 1.29 (m, 6H, $-CO_2CH_2CH_3$) ppm. CI/MS m/e: 385 (M^++1, 11%), 384 (-H, 3%), 383 ($-H_2$, 10%), 337 (7%), 309 (6%), 289 ($-H-OSO_2CH_3$, 100%), 215 (33%), 129 (26%). EI/HRMS m/e: (M^+-MeSO_3) 289.1433 (Calc. for $C_{18}H_{24}O_7S - CH_3O_3S = C_{17}H_{21}O_4$: 289.1440)

(3-[Bis(ethoxycarbonyl)methylidene])-tetracyclo[5.3.0.0^{2,5}.0^{4,8}]deca-9-ene **16**

A solution of **30** (1.8 g, 4.69 mmol) in EtOH (5 ml) was gradually added to a solution of NaOEt (obtained from 115 mg of Na, 5 m.at.) in EtOH (30 ml). After stirring for 2 h, ether was added and the reaction mixture washed with water (2x20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*, to give **16** as a light-yellow oil (purity 88% according to GLC). Flash chromatography (silicagel; n-hexane/EtOAc=3/1) gave **16** as a light-yellow oil (1040 mg, 3.61 mmol, 57%) (GLC: 98% pure).

UV(n-hexane): 196 nm (ε=5700, -CH=CH-), 223 nm (ε=11900, >C=C(COOEt)$_2$), 255 nm (ε=2450, CT-band). IR (CCl_4) ν: 3030 (-CH unsat.), 3000-2820 (-CH sat.), 1700 (-C=O ester unit), 1650 (>C=C< unsaturated ester) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 6.01 (d, 2H, H_9+H_{10}), 4.19 (dq, 4H, H_{13}), 3.44 (m, 2H, H_2+H_4), 2.98 (m, 4H, H_1+H_8+H_5+H_7), 1.73 (s, 2H, H_6), 1.28 (dt, 6H, H_{14}) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 173.3 (quat, 1C, C_{12}), 164.9 (quat, 1C, C_{12}), 135.7 (tert, 2C, C_9+C_{10}), 114.3 (quat, 1C, C_{11}), 96.0 (quat, 1C, C_3), 62.3 (tert, 1C, C_7), 60.2 (sec, 2C, C_{13}), 53.9 (tert,

2C, C_1+C_8), 50.3 (tert, 2C, C_2+C_4), 48.5 (tert, 1C, C_5), 35.0 (sec, 1C, C_6), 14.1 (prim, 2C, C_{14}) ppm. EI/MS m/e: 288 (M^+, 60%), 243 (-H, -CO_2, 57%), 214 (-H, -$O_2C_2H_5$, 40%), 196 (-(2xH_2), -(2xCO_2), 75%), 168 (50%), 141 (93%), 128 (43%), 115 (58%). EI/HRMS m/e: 288.1365 (Calc. for $C_{17}H_{20}O_4$: 288.1361).

(3-[Bis(ethoxycarbonyl)methylidene])-tetracyclo[5.3.0.$0^{2,5}$.$0^{4,8}$]decane **31**

A solution of **16** (300 mg, 1.04 mmol) in methylacetate (50 ml) containing a catalytic amount of Pt (10% on active carbon) was hydrogenated in H_2-atm of 40 lbs/inch^2 (ca. 2.5 atm.) using a Parr apparatus. After about 1 h complete transformation into **31** was observed (GC). The catalyst was removed by filtration over hyflo and the solvent evaporated *in vacuo* at r.t., to give **31** (296 mg, 1.02 mmol, 98%) as a clear and colorless oil (GLC: >99% pure).

UV(n-hexane): 228 nm (ε=12800, >C=C(COOEt)$_2$). IR (CCl_4) ν: 3000-2820 (-CH sat.), 1700 (-C=O ester unit), 1640 (>C=C< unsaturated ester) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 4.20 (q, 4H, H_{13}), 3.31 (m, 2H, H_2+H_4), 2.51 (m, 3H, H_1+H_8+H_5), 2.43 (m, 1H, H_7), 1.79-1.69 (m, 4H, H_9+H_{10}), 1.69 (s, 2H, H_6), 1.25 (t, 6H, H_{14}) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 172.8 (quat, 1C, C_{12}), 164.7 (quat, 1C, C_{12}), 113.7 (quat, 1C, C_{11}), 95.7 (quat, 1C, C_3), 60.1 (sec, 2C, C_{13}), 50.8 (tert, 2C, C_2+C_4), 49.4 (tert, 1C, C_5), 49.3 (tert, 2C, C_1+C_8), 39.1 (tert, 1C, C_7), 33.6 (sec, 1C, C_6), 28.8 (sec, 2C, C_9+C_{10}), 13.8 (prim, 2C, C_{14}) ppm. EI/MS m/e: 290 (M^+, 40%), 244 (-C_2H_5OH, 100%), 216 (-H, -$CO_2C_2H_5$, 70%), 198 (-H, -$CO_2C_2H_5$, -H_2O, 51%), 170 (23%), 130 (18%). EI/HRMS m/e: 290.1517 (Calc. for $C_{17}H_{22}O_4$: 290.1518).

2.5 References and notes

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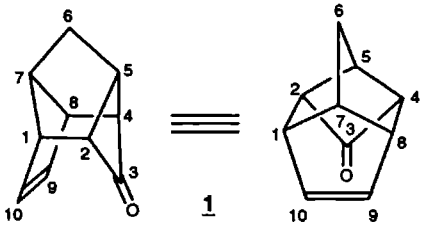
CHEMICAL BEHAVIOR OF 2,9-CARBONYL-BREND-4-ENE AND 2,9-CARBONYL-1,8-HOMO-BREND-4-ENE

3.1 Introduction

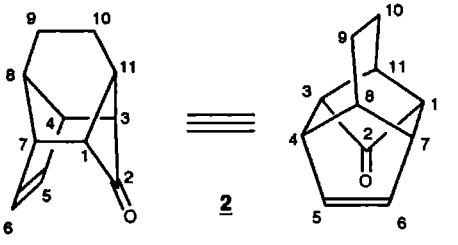
In chapter 2 the synthesis of 2,9-carbonyl-brend-4-ene and its 1,8-homo and 1,8 bishomo analog has been described. The interesting structural feature of these compounds is that the olefinic part and the carbonyl group are positioned orthogonally and in close proximity, implying that in certain reactions both functions may participate. In chapter 2 an electronic interaction between the two orthogonal π-functions was established. In this chapter the chemical interaction between these functions will be considered, as well as the specific reactivity of the olefinic bond and the carbonyl group. Derivatization of either of these functions may lead to new polycyclic structures having two functionalities at a close distance. In this context a derivative which would be suitable for X-ray diffraction analysis, is of great interest as it would enable the precise determination of the intramolecular distance of both functions. It should be explicitly noted that the compounds 1 and 2 are not suitable for this purpose because of their high volatility even in the crystalline form. Moreover, suitable crystals for an X-ray analysis could not be obtained due to the high solubility of these compounds in organic solvents.

As already pointed out in chapter 2 polycycles 1 and 2 are considerably strained. According to MM2 calculations the strain energy amounts to 65 kcal/mole for 1 and 70.7 kcal/mole for 2. For polycycles with such high energy content, reactions may be expected that are primarily driven by relief of ring strain, an interesting aspect worth investigating.



Tetracyclo[5.3.0.0^{2,5}.0^{4,8}]dec-9-en-3-one

(2,9-carbonyl-brend-4-ene)



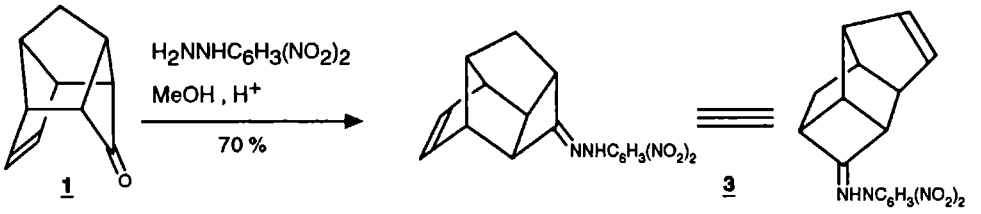
Tetracyclo[5.4.0.0^{3,11}.0^{4,8}]undec-5-en-2-one

(2,9-carbonyl-1,8-homo-brend-4-ene)

3.2.1 Reactions under acidic conditions.

During attempts to prepare a dinitrophenylhydrazone from 1, using standard conditions[1], a crystalline product was obtained in 70% yield. The spectral data revealed that the symmetrical skeleton of 1 had undergone rearrangement. Detailed spectral analysis suggested structure 3 for this product. Unambiguous confirmation of this structure was obtained from an X-ray diffraction analysis[2] (Scheme 3.1). Knowing the correct structure of 3, the asymmetric pattern of the ^{1}H-NMR

Scheme 3.1



1 3

signals, which is of importance for the recognition of other rearrangement products obtained in the present study, could now be explained (*vide infra*).

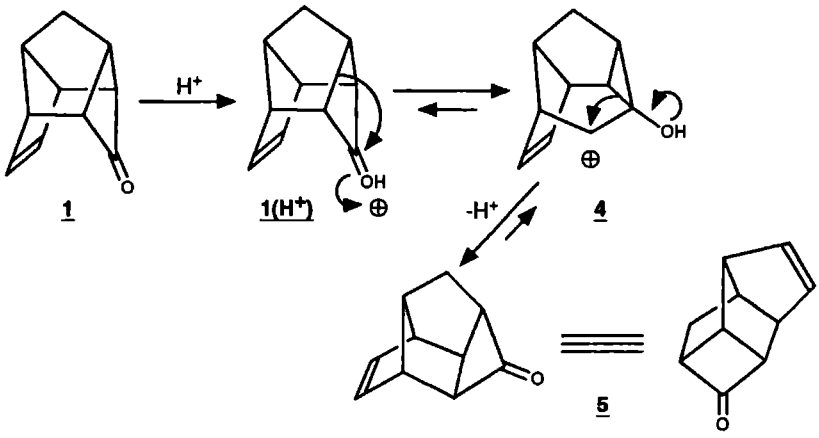
All attempts to prepare other imine-type derivatives using standard methods, *e.g.* by treatment of **1** with hydroxylamine (H_2NOH)[1,3], semicarbazide ($H_2NNHC(O)NH_2$)[4] and tosylhydrazine ($H_2NNHSO_2C_6H_4CH_3$)[5] all failed. In all cases starting material was recovered unchanged.

The formation of rearranged product 3 can be rationalized by invoking a cyclobutyl-cyclopropylcarbinyl cation rearangement[6], as is depicted in scheme 3.2. Initial protonation leads formally to a cyclobutyl cation, which then undergoes a 1,2-shift to produce cyclopropyl carbinyl cation 4, which on a subsequent 1,2-shift gives the ultimate product 5. This product apparently reacts with the hydrazine reagent in the usual fashion to give hydrazone 3. This skeletal rearrangement of 1 to 5 goes along with a relief of strain (SE of 1: 65.1 kcal/mole, SE of 5: 64.2 kcal/mole).

These initial experiments indicate that the cyclobutanone unit in 1 shows an unusual behavior. The propensity of compound 1 to undergo skeletal rearrangement is particularly noteworthy. To further explore the reactivity toward acidic reagents carbonyl brendene 1 and at a later stage also its more strained homolog 2, were exposed to a variety of such reagents.

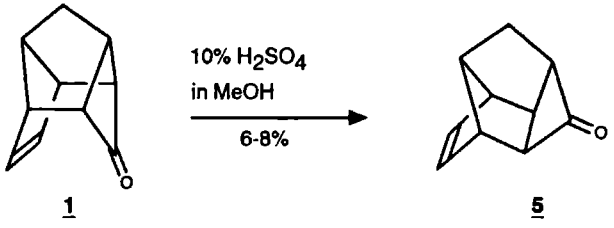
Using the same acidic conditions which led to the formation of the rearranged hydrazone 3

Scheme 3.2



viz. a 10% solution of sulfuric acid in methanol, but now in the absence of the hydrazine, tetracyclic ketone 1 again underwent rearrangement but only to a minor extent. After stirring for 1 h rearranged ketone 5 was isolated in a yield of only 6-8% (GLC)(Scheme 3.3). This result is indicative of an

Scheme 3.3

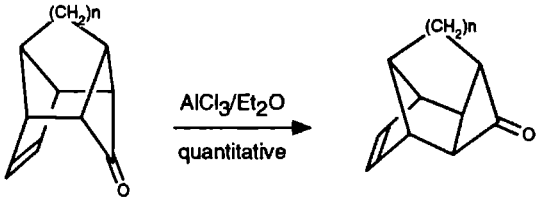


equilibrium between 1 and 5, which can be shifted toward 5 when for instance the formation of hydrazone 3 is possible (Scheme 3.1). The structure of 5 was established at a later stage from the reaction of 1 with aluminum chloride (*vide infra*).

The skeletal rearrangement of 1 was then investigated with the Lewis acid catalyst aluminum chloride. Treatment of 1 with anhydrous aluminum chloride in dry ether smoothly produced a new compound in 95% yield, which has the same molecular mass but which has lost the C_2-symmetry as was deduced from its ^{1}H- and ^{13}C-NMR spectra. The spectral features of this product resemble those of hydrazone 3 as far as the polycyclic unit is concerned. Structure 5 is proposed for this rearranged product on the basis of this similarity (Scheme 3.4). The olefinic protons appear in the ^{1}H-NMR as a slightly split signal, while in 1 they resonate as a sharp singlet. The carbonyl absorption in the IR spectrum is present at 1780 cm^{-1} for 5 and at 1762 cm^{-1} for 1. The mass spectra of 1 and 5 show very similar fragmentation patterns.

Substrate 2 with an ethylene bridge, shows a similar behavior as 1 toward aluminum chloride. When treated with a catalytic amount of anhydrous aluminum chloride in dry ether rearranged product 7 was obtained in 90% yield (Scheme 3.4). Again the NMR spectral characteristics clearly reveal that the molecular symmetry of the starting material is no longer present.

Scheme 3.4

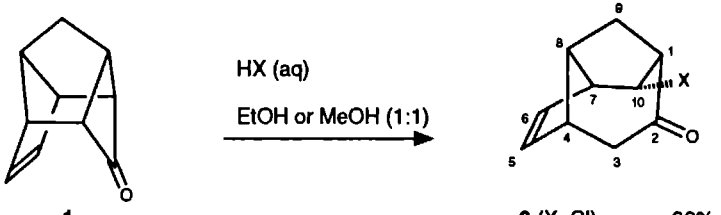


1 n=1
2 n=2

5 n=1
7 n=2

An entirely different behavior was observed when 2,9-carbonyl-brend-4-ene 1 was treated with concentrated hydrochloric acid in an equal volume of ethanol. A new product was isolated in 96% yield, which had a polycyclic skeleton definitely different from 5. Its structure 8 was unambiguously established by X-ray diffraction analysis[2] (Scheme 3.5). In a similar fashion reaction

Scheme 3.5



1

8 (X=Cl) 96%
9 (X=Br) 43%

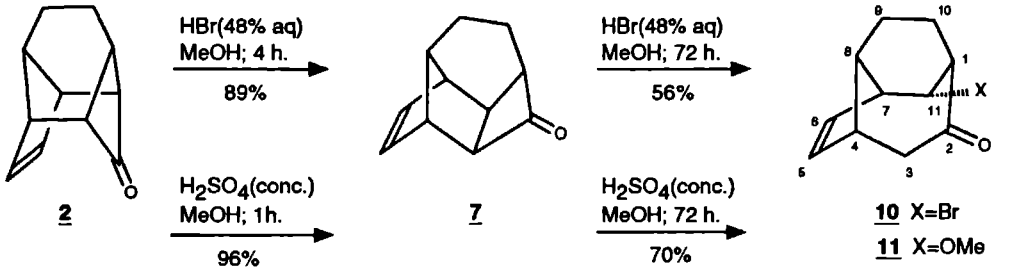
of 1 with concentrated aqueous hydrobromic acid in methanol gave product 9 in 43% yield (Scheme 3.6). The structure of this product was again secured by means of an X-ray diffraction analysis[2].

The homolog of 1, 2,9-carbonyl-1,8-homo-brend-4-ene 2, was also treated with concentrated aqueous hydrobromic acid in methanol. After a reaction time of 4 h compound 7 was detected in 89% (cap. GC) (Scheme 3.6). This product had the same retention time as the one obtained in the rearrangement reaction induced by anhydrous aluminumchloride.

Prolonged treatment of 2 with concentrated aqueous hydrobromic acid in methanol(72 h) gave an additional product in 56% yield, to which on the basis of spectral resemblance with 8 and 9 structure 10 was assigned (Scheme 3.6). Confirmative evidence was provided by a detailed ^{1}H-NMR spectral analysis using the NOE technique. The relevant data of this analysis are summarized in Section 3.6.

Compound 2 was also treated with concentrated sulfuric acid in methanol, which for 1, as

Scheme 3.6



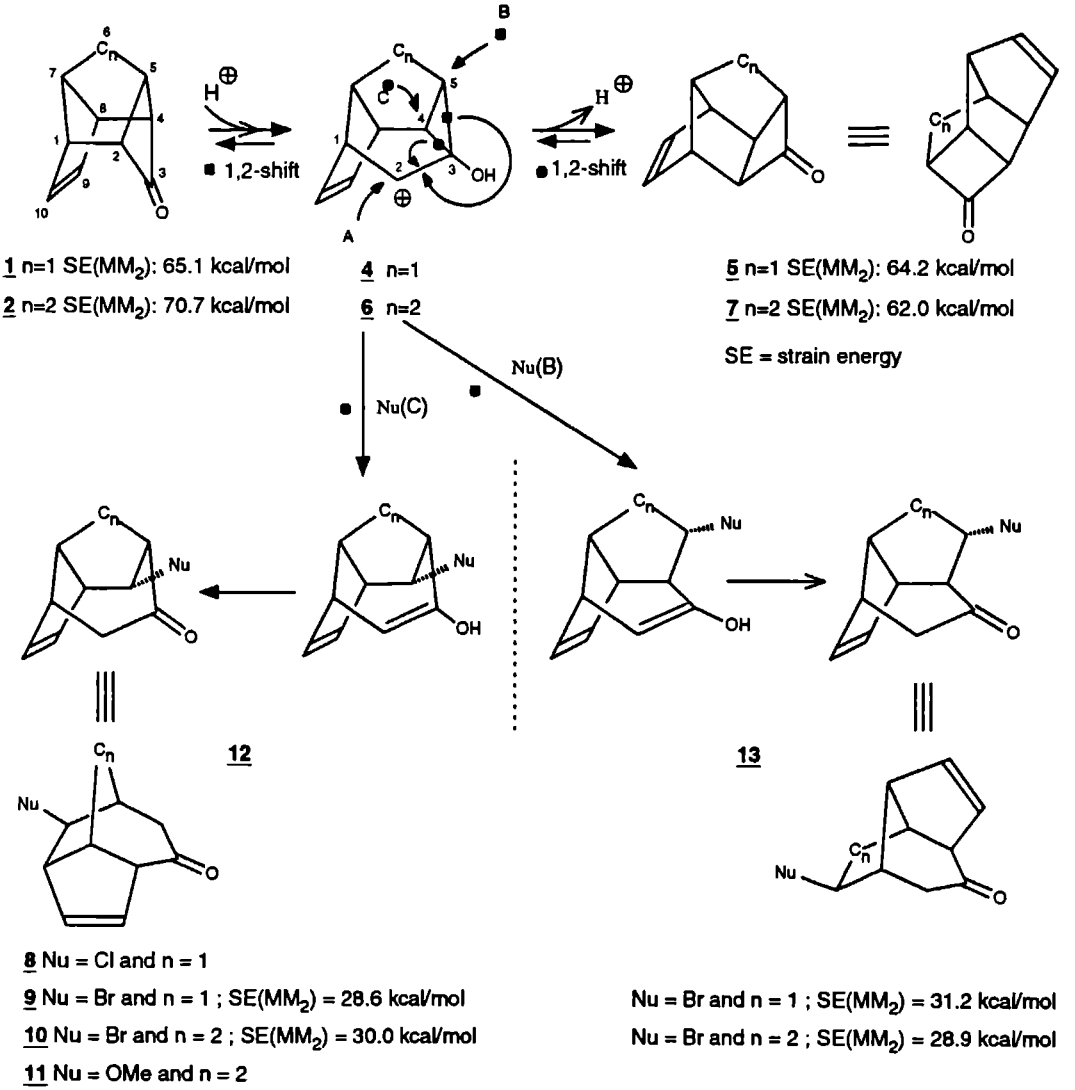
described above, gave only a minor amount of rearranged ketone **5**. However, reaction of **2** with concentrated sulfuric acid in methanol (1:4) gave the corresponding rearranged ketone **7** after 1 h in almost quantitative yield (GLC). This product was identical to that obtained from the reaction of **2** with aluminum chloride (*vide supra*). Prolonged treatment of **2** with methanolic sulfuric acid (72 h) gave a new product in a yield of 70% (GLC), to which on the basis of a detailed ^{1}H-NMR analysis (Section 3.7) structure **11** was assigned (Scheme 3.6). A comparison of ^{1}H- and ^{13}C-NMR data of **11** with those of bromide **10** (Table 3.1) clearly supports the correctness of this assignment.

Table 3.1 The NMR-data of **10** and **11**

^{1}H				^{13}C			
11		**10**		**11**	**10**		
proton	δ	proton	δ	δ	δ	multiplicity	assign.
2	5.78	2	5.83	213	211	quat	C=O
3	5.71	3	5.73	136	136	tert	olefin
		13	4.07	134	134	tert	olefin
1	3.07	1	3.23	76	54	tert	C-Nu
6	3.04	6	3.05	56		prim	MeO
4	2.77	4	2.76	49		tert	
7	2.77	7	2.73	48	49	tert	
12	2.66	12	2.65	46	46	sec	
13	2.60			44	44	tert	
		8	2.36	38	38	tert	
5	2.26	5	2.27	18	19	sec	bridge
		11	2.23	17	17	sec	bridge
8,9,10,11	2.25-1.75	10	2.05				
		9	1.93				

The incorporation of a halide or methoxy function in the rearranged products as observed in the reaction of ketones 1 and 2 with hydrogen halides or of 2 with sulfuric acid in methanol can be explained by nucleophilic trapping of the cationic intermediate initially formed in the cyclobutyl-cyclopropyl carbinyl rearrangement, *viz.* 4 and 6 (Scheme 3.7). Attack of the nucleophile at this

Scheme 3.7 The rearrangement to products with an incorporated nucleophile



1 n=1 SE(MM_2): 65.1 kcal/mol
2 n=2 SE(MM_2): 70.7 kcal/mol

4 n=1
6 n=2

5 n=1 SE(MM_2): 64.2 kcal/mol
7 n=2 SE(MM_2): 62.0 kcal/mol
SE = strain energy

12

13

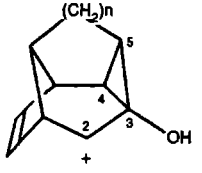
8 Nu = Cl and n = 1
9 Nu = Br and n = 1 ; SE(MM_2) = 28.6 kcal/mol
10 Nu = Br and n = 2 ; SE(MM_2) = 30.0 kcal/mol
11 Nu = OMe and n = 2

Nu = Br and n = 1 ; SE(MM_2) = 31.2 kcal/mol
Nu = Br and n = 2 ; SE(MM_2) = 28.9 kcal/mol

intermediate may be envisaged at all three different electrophilic positions *viz.* A, B and C. Attack at position A would lead to a cyclopropanol constrained in a strained system and is apparently

unfavorable as no such products were detected. Attack at the cyclopropane carbon positions B and C are quite conceivable as this leads to cyclopropane ring opening and the ultimate formation of the more relaxed structures **12** and **13**, respectively. The observation that only products related to **12** are formed in this rearrangement reaction shows that this cyclopropane ring opening occurs regiospecifically by initial attack of the nucleophile at the C-position in **4** or **6**. The regiospecificity of this process of cyclopropane ring cleavage is certainly not solely determined by thermodynamic factors since only ketone **1** (n=1) eventually leads to the thermodynamically most stable enone **12** (n=1). Ketone **2** also gives exclusively enone **12** which however, according to MM2 calculations, is less stable than its isomer **13**. Two other factors may considerably affect the direction of ring opening. Firstly, the asymmetry of the intermediate carbocation makes that nucleophilic attack at both positions B and C are sterically not equivalent. Molecular models show that for **4** (n=1) steric approach control does not seem important as steric differences are minimal. However, for **6** (n=2) the ethylene bridge clearly hampers attack at position B more severely than at position C. Although steric effects may play a role, strain within the structures **4** and **6** is probably of decisive importance. MINDO/3 minimized geometries of both **4** and **6** clearly show that the longest and thus weakest bond within the cyclopropane ring will break during the bond cleavage process (Table 3.2).

Table 3.2 Bond length (l), partitioning energy (E_{ab}) and bond index (W_{ab}) for the bonds of the cyclopropane part within the structures **4** and **6**, according to MINDO/3 calculations.



4 n=1
6 n=2

structure	**4**			**6**		
bond	3-4	4-5	3-5	3-4	4-5	3-5
l(Å)	1.66	1.47	1.62	1.67	1.47	1.61
E_{ab}(eV)	-8.85	-15.46	-9.79	-8.38	-15.64	-10.27
W_{ab}	0.627	1.079	0.668	0.601	1.075	0.695

It may therefore be concluded that the acid catalyzed rearrangement of ketones **1**, **2** and **5**, **7** followed by nucleophilic trapping is a process which is mainly determined by structural features of the intermediate cyclopropylcarbinyl cation **4** and **6**.

The difference in chemical behavior observed for **1** and **2** in their reaction with a nucleophilic

acid (HBr) and methanolic sulfuric acid can be explained by the differences in strain energy of both polycycles and their respective rearranged structures 5 and 7. For 2 the relieve of strain energy is considerably higher than for 1 which corresponds with a greater propensity of 2 for rearrangement.

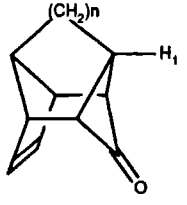
3.2.2 Reactions at the carbonyl function

3.2.2.1 The Grignard reaction.

Nucleophilic reactions at the carbonyl function of 2,9-carbonyl-brend-4-ene 1 and its homolog 2,9-carbonyl-1,8-homo-brend-4-ene 2 have the interesting feature that the approach of the reactant will be directed by the olefinic group in close proximity. Because of this olefinic moiety *endo* approach of any reagent will be severely hampered and consequently reaction from the *exo* side will be preferred. Another aspect that needs to be considered involves the change of hybridization at the carbonyl carbon during the nucleophilic addition process, forcing the negative oxygen atom of the carbonyl toward the double bond and causing an increase of the strain energy of the system due to both van der Waals and Coulomb interactions.

The *exo* approach of a nucleophile will ideally occur at an angle of about 110° in relation to the plane of the carbonyl group[7]. However, with RLi the reactions proceed via a four-centered transition structure wherein lithium coordinates with the carbonyl. The angle of attack for these reagents will be smaller than that for "free" nucleophiles because of the polarization of the carbonyl by metal coordination and the cyclic nature of the transition structure. Model calculations, in which LiH or CH_3Li (or it's dimer) reacts with a carbonyl, suggest an angle of attack between 94° and 97° [8]. Structural analysis of 1 and 2 reveals that some interference of a nucleophilic reagent with H_1(see Figure 3.1) may be encountered.

Figure 3.1



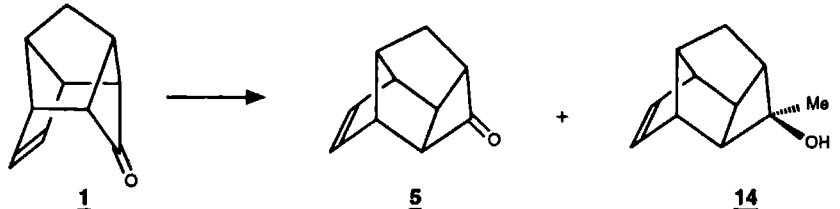
n=1 1

n=2 2

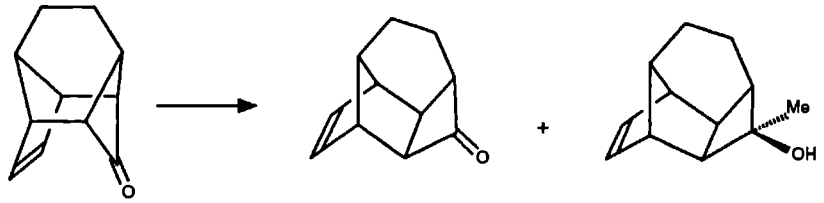
The reaction of 2,9-carbonyl-brend-4-ene 1 with methylmagnesium iodide gave an unexpected result. After a reaction time of 10 minutes at room temperature no addition product but solely a complete rearrangement to the 2,9-carbonyl-brex-4-ene structure 5 (85% yield) was

observed (Scheme 3.8). When the reaction was carried out under reflux conditions in diethyl ether for 1.5 h, an addition product was formed, in 75% yield (GLC) along with some 2,9-carbonyl-brex-4-ene **5** (18%, GLC). The addition product has structure **14** (Scheme 3.8) as was deduced from a detailed spectral analysis. Homolog **2** showed a similar behavior (Scheme 3.8). Grignard reaction

Scheme 3.8 Reactions with MeMgI



1	**5**	**14**
MeMgI,ether,20°C	100%	-
MeMgI,ether,reflux	18%	75%



2	**7**	**15**
MeMgI,ether,r.t.	100%	-
MeMgI,ether,reflux	85%	10%
MeMgI,THF,reflux,30h	13%	83%

with methylmagnesium iodide at room temperature gave only rearrangement to 2,10-carbonyl-1,9-homo-brex-4-ene **7** in quantitative yield. When carried out under reflux conditions in THF for 30 h the addition product of **7**, *viz.* alcohol **15**, was formed in 83% (GLC). When heated under reflux in ether for 48 h only 10% (GLC) of this adduct was obtained, the remainder was 2,10-carbonyl-1,9-homo-brex-4-ene **7**.

The precise structure of adduct **15**, especially the stereochemistry of the OH function was deduced from a detailed analysis of its ^{1}H-NMR spectra by selective decoupling experiments and using lanthanide shift reagent Eu(fod)$_3$. Complexation of the lanthanide with the OH group will cause a large shift of those protons which are connected to a neighboring carbon atom of the polycyclic structure, when they are in a *syn* orientation. Since this indeed was found, it must be concluded that structure **15** has an *endo* oriented OH function (For structure **14** this has not been established. However, it may be expected that it will behave the same as **15**).

Clearly, the reaction of methylmagnesium iodide with both enones 1 and 2 does not lead to addition but instead initiates a fast rearrangement to the less strained isomers, brexenones 5 and 7, respectively. These brexenones then undergo slow Grignard addition to form the corresponding endo-alcohols 14 and 15. This remarkable result can be explained by assuming that the Grignard reagent has acted as Lewis Acid catalyst in the skeletal rearrangement of the brendene to the brexene system. Initial complexation of the Grignard reagent with the carbonyl oxygen results in an increase of positive charge at the cyclobutyl carbonyl carbon. This increase in electrophilicity at the carbon is apparently large enough to trigger a fast cyclobutyl/cyclopropylcarbinyl cation rearrangement to give the observed brexenones (Scheme 3.7). The observation that this rearrangement is apparently much faster than the nucleophilic addition of a Grignard reagent is quite unique as cyclobutanones are known to react rapidly in nucleophilic addition reactions due to release in angle strain going from an sp^2 hybridization in the ketone to an sp^3-hybridization in the addition product. It shows that brendenones 1 and 2 are highly unstable compounds which rapidly rearrange to more relaxed structures. The observation that the rearranged ketones 5 and 7 also react sluggishly with methylmagnesium iodide is also not expected. Although steric hindrance may play a role, no satisfactory explanation is at hand yet.

The exclusive formation of endo-alcohols 14 and 15 is readily understood from molecular modeling. Endo-addition to the carbonyl functions in 5 and 7 is severely hindered by the norbornene moiety.

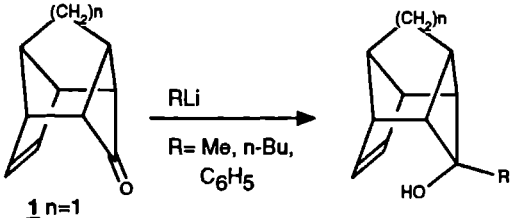
3.2.2.2 Reaction with organo lithio compounds.

A rearrangement such as observed above could be avoided by using an organometallic reagent which has no Lewis acid character, *viz.* organolithium compounds. Indeed, reaction of substrate 1 with methyllithium gave alcohol 16, which still contains the original brendene structure, in 75% yield. The structure of this addition product is immediately apparent from the symmetry features in its NMR spectra. In a similar manner homolog 2 gave an addition product with methyllithium (yield 94%) in which the polycyclic skeleton has also retained its original structure. Reaction of both substrates 1 and 2 with butyllithium and phenyllithium gave the corresponding *endo* alcohols in high yields (Scheme 3.9). In neither case any rearranged product was observed.

In all cases studied the addition of organolithio compounds to both 1 and 2 are stereospecific processes. No *exo* alcohols are formed due to complete steric blocking of *exo* addition by the olefinic moiety.

The *endo* alcohols are characterized by an infrared band below 3600 cm^{-1}, attributable to an OH function which is involved in hydrogen bonding with the olefinic π system[9a]. In comparison with the starting carbonyl brendenes 1 and 2, the ^{1}H-NMR signals of the olefinic protons in the adducts

Scheme 3.9 Reactions with organolithio compounds



1 n=1
2 n=2

		yield
16 R=Me;	n=1	75%
17 R=Me;	n=2	94%
18 R=n-Bu;	n=1	86%
19 R=n-Bu;	n=2	97%
20 R=C_6H_5;	n=1	89%
21 R=C_6H_5;	n=2	92%

are located at lower field, consistent with this intramolecular hydrogen bonding[9b]. The ^{13}C-NMR signals of the olefinic carbon atoms in the alcohols also appear downfield from the corresponding signals of the precursor ketones (Table 3.3).

Furthermore, the ^{13}C-NMR spectra proved the symmetry for the brendene structures by showing n-3 signals (that is 7 for 1, 8 for 2 and 16, 9 for 17, 11 for 18, 12 for 19, 13 for 20 and 14 for 21).

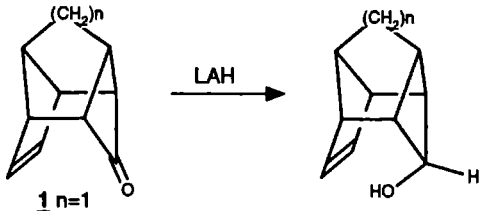
Table 3.3 ^{1}H-NMR values for the olefinic protons, ^{13}C-NMR values for the olefinic carbons and IR values for the free OH-band of the compounds 1, 2 and 16-23

No	^{1}H-NMR (ppm)	^{13}C-NMR (ppm)	IR (cm^{-1})	No	^{1}H-NMR (ppm)	^{13}C-NMR (ppm)	IR (cm^{-1})
1	6.16	137.82		2	6.48	143.33	
22	6.47	140.25	3598	23	6.81	144.99	3598
16	6.52	141.25	3580	17	6.86	146.20	3587
18	6.51	141.37	3580	19	6.85	146.17	3582
20	6.64	141.15	3560	21	6.93	145.81	3560

3.2.2.3 Hydride reduction

The reduction of 2,9-carbonyl-brend-4-ene 1 and its homolog 2,9-carbonyl-1,8-homo--brend-4-ene 2 with lithium aluminum hydride gave smooth formation of the *endo* alcohols 22 and 23 in yields of 80% and 93%, respectively (Scheme 3.10). No skeletal rearrangement or formation of any *exo* alcohol was observed. The OH band at 3598 cm^{-1} in the IR-spectrum of 22 and 23 is again indicative of hydrogen bonding[9] between the OH function and the π system, as is the downfield shift for the olefinic protons and carbons in the ^{1}H- and ^{13}C-NMR spectra in comparison with the carbonyl brendenes 1 and 2 (Table 3.3). The amount of signals (n-3) in the ^{13}C-NMR spectra leads to

Scheme 3.10 Reactions with lithium aluminum hydride



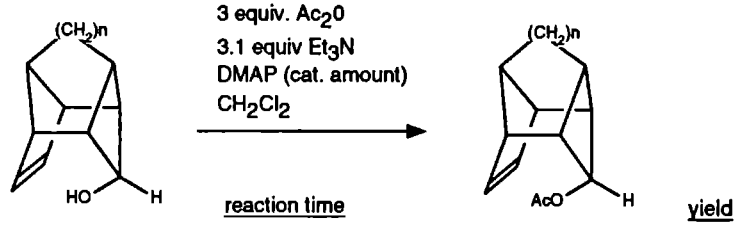
1 n=1
2 n=2

	yield
22 n=1	80%
23 n=2	93%

the conclusion that no rearrangement has taken place and that the symmetrical brendene structures are still present.

The question now arises whether the *endo* alcohol function in 22 and 23 will still be reactive enough for functionalization being so close to the olefinic unit. It was found that alcohol 22 as well as 23 can be acetylated using acetic anhydride in the presence of triethylamine and dimethylamino-pyridine in high yields by employing rather long reaction times (Scheme 3.11). The spectral features of the acetates 24 and 25 still reveal the high symmetry of these compounds, proving that no skeletal rearrangement has occurred.

Scheme 3.11 Synthesis of acetates

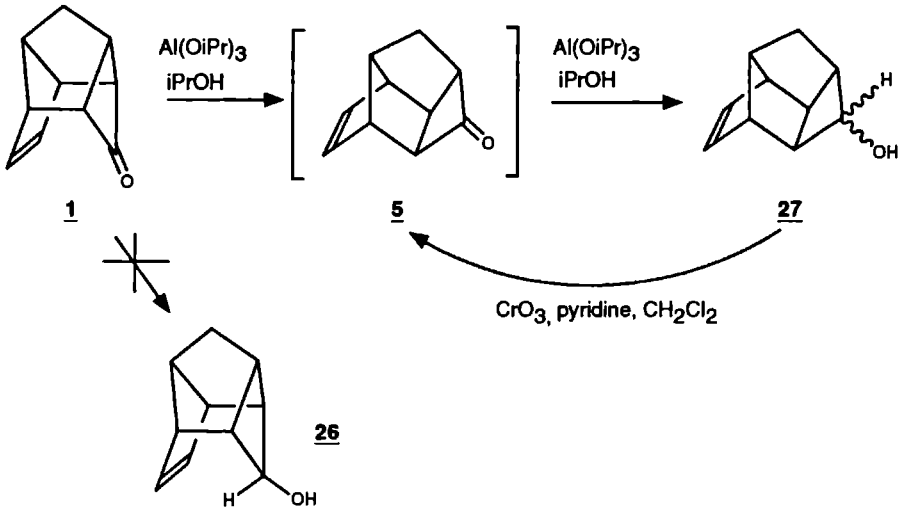


	reaction time		yield
22 n=1	1 day	24 n=1	96%
23 n=2	2 days	25 n=2	92%

As a possible means to obtain the thermodynamically more stable *exo* alcohol 26 from enone 1, the Meerwein Pondorf Verley (MPV) reaction was also considered. Using freshly prepared aluminum isopropoxide in isopropyl alcohol it was found however, that under the conditions of this reaction initial skeletal rearrangement to 2,9-carbonyl-brex-4-ene 5 takes place, followed by subsequent reduction of 5 to 2,9-methano-brend-4-ene-10-ol 27 (Scheme 3.12). The stereochemistry of the alcohol function in 27 could not be established. Oxidation of 27 with CrO_3/pyridine gave 2,9-carbonyl-brex-4-ene 5, proving that the MPV-reduction product indeed has the polycyclic framework shown.

The reduction of 1 with a dissolving metal, *viz.* Li in NH_3 (liq.) was also investigated with the

Scheme 3.12 The Meerwein-Pondorff-Verley reduction of 1

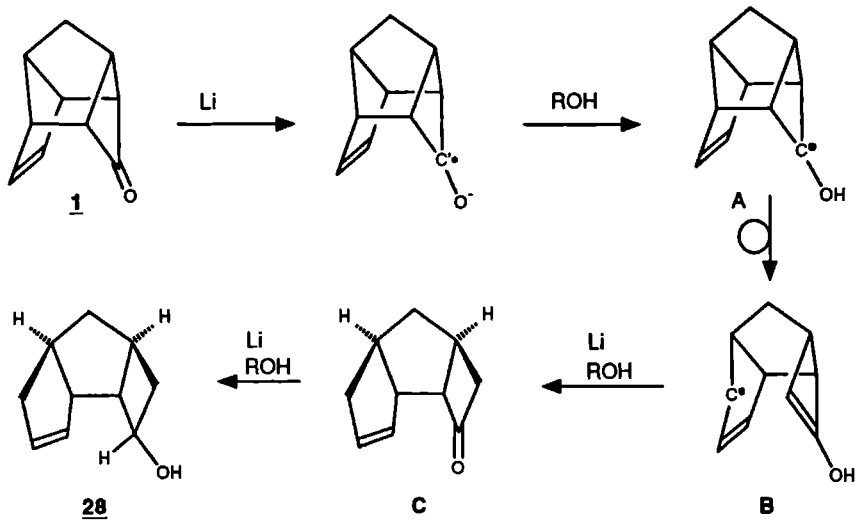


same aim namely to obtain 10-*exo*-hydroxy-2,9-methano-brend-4-ene **26** instead of 10-*endo*-hydroxy-2,9-methano-brend-4-ene **22**. A reduction product was indeed observed, however, spectral analysis immediately showed that the original polycyclic skeleton had undergone bond cleavage. The isolation of a single product in good yield (73%) showed that this bond cleavage reaction is not a random process. A detailed NMR spectral analysis using the COSY technique revealed structure **28** for this product (Section 3.8). The formation of this tricyclic alcohol can conveniently be explained by the mechanistic scheme as depicted in Scheme 3.13. After the initial radical anion formation by electron transfer from the metal to the carbonyl group in **1** followed by protonation, **A** undergoes ring cleavage to form allylic radical **B**. This bond cleavage not only relieves strain energy but it also leads to the formation of a more stable allylic radical. After a second electron transfer and protonation ketone **C** is formed. Since excess lithium metal is present, **C** will be further reduced to tricyclic alcohol **28** (Scheme 3.13).

3.2.2.4 Reaction with hydrazine.

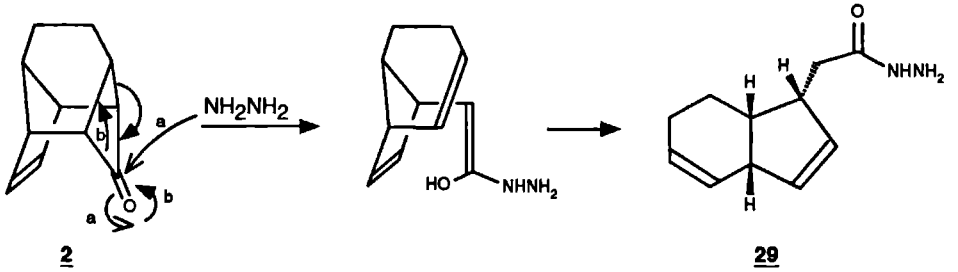
In section 3.2.1 the reaction of both 2,9-carbonyl- brend-4-ene **1** and its homolog **2** with various amine reagents was described. For both ketones no imine formation was observed without initial rearrangement. In all cases studied sofar acid catalysis was applied. In view of the sensitivity of **1** and **2** toward acids and to avoid skeletal rearrangement, it was decided to study the addition of amines in the absence of such an acid catalyst. Hydrazine was selected as the first amine and 2,9-carbonyl-7,8-homo-brend-4-ene **2** as the substrate because of its availability at that time.

Scheme 3.13 Mechanism for the reaction of 1 with Li in NH_3



Treatment of 2 with hydrazine in ethanol in the presence of molecular sieves(3 Å) under reflux conditions, gave, after 53 h, a new product in 86% yield (isolated 49%), whose basic structure was considerably different from the brendene and brexene polycycles. A detailed NMR spectral analysis, involving 2D COSY experiments, revealed that structure 29 can be assigned to this compound (Section 3.9). Its formation is outlined in scheme 3.14. The initial reaction of hydrazine with the carbonyl group is followed by a cleavage of the polycyclic system involving two bonds. Relief of strain is undoubtedly the driving force of this peculiar reaction.This observation of a very efficient

Scheme 3.14 The formation of hydrazide 29



bond cleavage in 2 initiated by a simple hydrazine addition to its carbonyl function clearly demonstrates the chemical lability of this highly strained tetracyclic system. Although not studied in detail yet, no such fragmentation is observed for 1 when treated with amines. In all cases studied sofar only starting material was recovered.

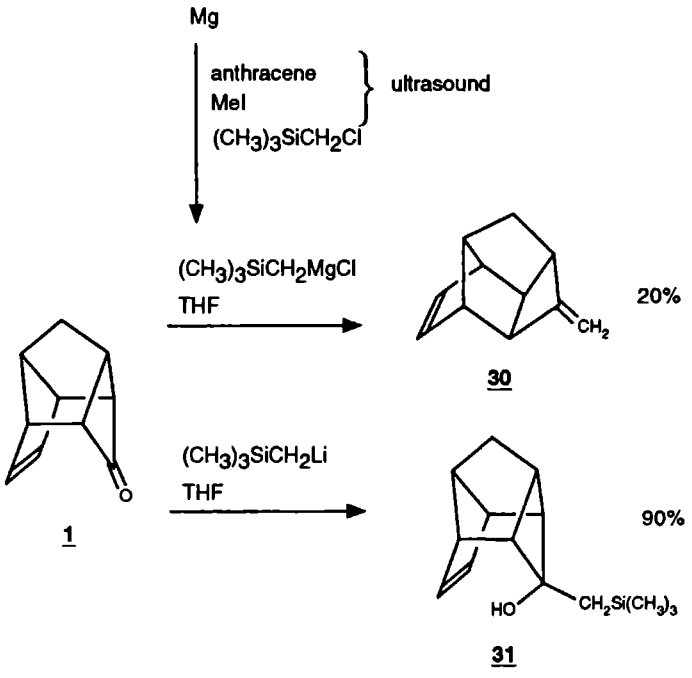
3.2.2.5 The Peterson and Wittig reaction.

An olefination reaction of 2,9-carbonyl-brend-4-ene **1** and its homolog **2** would lead to polycyclic systems containing two orthogonal olefinic π bonds again in close proximity. Our interest in the chemistry of these compounds prompted us to attempt the synthesis of these dienes. Obvious routes for the olefination of carbonyl compounds are the Peterson and Wittig reaction.

The Peterson olefination of **1** was first attempted with (trimethylsilyl)methylmagnesium chloride which was obtained from α-chlorosilane and highly reactive magnesium generated from magnesium, anthracene and methyl iodide using ultrasonic activation[10]. Indeed a bis-olefin was obtained in 20% yield, however ^{1}H-NMR spectral data immediately indicated that this diene did not contain the symmetric brendene skeleton but a brexene-type polycyclic system (Scheme 3.15). Detailed spectral analysis showed this diene to have structure **30**. The formation of **30** can conveniently be explained by assuming initial skeletal rearrangement of **1** into **5** induced by the Grignard reagent in a similar way as observed earlier for **1** with methylmagnesium iodide (Scheme 3.8). In a subsequent reaction Peterson olefination of **5** then leads to the observed diene **30**. Further support for structure **30** was obtained from the Wittig olefination of **5**. When 2,9-carbonyl-brex-4-ene **5** was reacted with methylene(triphenyl)phosphorane diene **30** was obtained in 64% yield, thus providing an unambiguous proof of the structure of bis-olefin **30** (Scheme 3.15).
As shown in section 3.2.2 organolithium reagents do not cause skeletal rearrangements. Therefore, the Peterson reaction was tried with (trimethylsilyl)methyllithium (prepared by the reaction of α-chlorosilane with lithium metal under reflux conditions) in THF. The reaction produced a new product in almost quantitative yield. The ^{1}H-NMR spectrum showed the familiar symmetry features characteristic for the brendene system, but also the presence of a (trimethylsilyl)methyl group, while in the infrared spectrum a clear OH absorption was observed. A D_2O exchange experiment showed that the OH signal in the ^{1}H-NMR spectrum is present at 5.15 ppm. Furthermore, the experiment revealed a coupling between the OH group and the methylene signal of the newly introduced silyl group. A ^{1}H-NMR spectrum without TMS as an internal standard gave the position of the methyl signals of the newly introduced silyl group at 0 ppm. This information led to the conclusion that hydroxy compound **31** had been obtained (Scheme 3.15). The desired elimination of trimethylsilanolate had not taken place. Attempts to accomplish this elimination by treatment with thionyl chloride, acetyl chloride or potassium hydride (according to the literature[12] these reagents should lead to olefin formation) all resulted in complex reaction mixtures in which the desired bis-olefin could not be detected.

The Wittig reaction using methylene(triphenyl)phosphorane took a more successful course. After a rather long reaction time (2 days) at room temperature the desired bis-olefin **32** was obtained in 45% yield (GC) while a considerable amount of starting ketone **1** was recovered. The yield of **32** could be considerably improved (to 80% GLC) by using a twofold excess of Wittig reagent (Scheme

Scheme 3.15 The Peterson reaction of 1

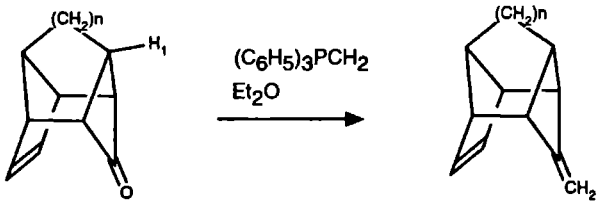


3.16).

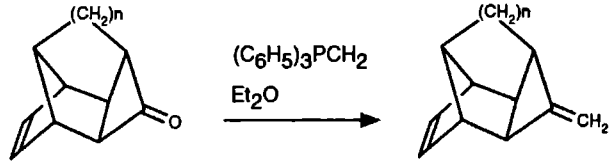
Bis-olefin 32 is a very volatile compound. Its NMR spectra again reveal a high degree of symmetry. The olefinic protons show up as two singlets at 6.0 and 4.3 ppm, respectively; the remaining protons appear between 3 and 1.5 ppm. It should be noted that this compound is distinctly different from the bis-olefin 30 derived from 2,9-carbonyl-brex-4-ene 5.

In a similar fashion using again 2 equiv. of phosphorane, the Wittig olefination of 2 was attempted. However, after 2 days reaction time no product formation had taken place (Scheme 3.16). Assuming that the addition of the non-stabilized methylene phosphorane to the ketone function is an irreversible process this last result shows that the ketone function in 2 is apparently less apt to react with phosphorous ylides than that in 1. This decreased reactivity is not well understood yet but may be both of steric and electronic origin. The outbending effect of the ethylene bridge in 2 as compared with 1 brings the carbonyl carbon closer to the olefinic function which may decrease the electrophilicity at the carbonyl carbon by p^{π}-p^{π} orbital overlap between the olefinic and the carbonyl functions. On the other hand models show that in 2 bridgehead proton H_1 (Figure 3.1) is bent slightly more toward the ketone than in 1 therefore an increased hampering of the attack of the bulky phosphorane ylid at the *exo* face of the ketone function may be expected. It is worth noting that the rearranged structure, namely 2,10-carbonyl-1,9-homo-brex-4-ene 7 smoothly reacts with the Wittig

Scheme 3.16 The Wittig reaction with 1, 2, 5 and 7



1 n=1	1 eq. 2 days	32 n=1 45%
1 n=1	2 eq. 2 days	32 n=1 80%
2 n=2	2 eq. 2 days	no reaction



5 n=1	2 eq. 2 h.	30 n=1 quant.
7 n=2	2 eq. 1 h.	33 n=2 quant.

reagent to give bis-olefin 33 in a high yield (90%)(Scheme 3.16).

3.2.3 Reactions with the olefinic function.

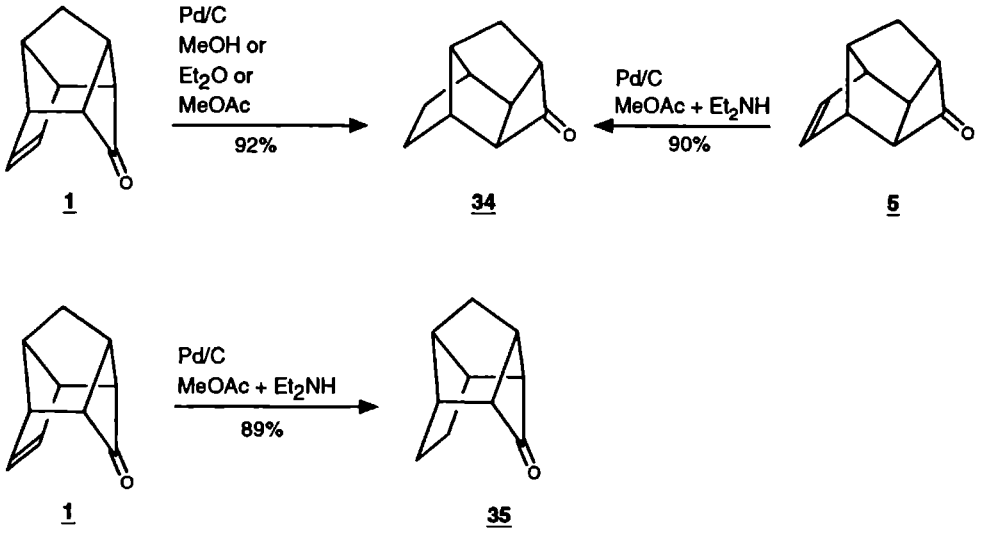
3.2.3.1 Selective reduction.

The catalytic reduction of the double bond in 2,9-carbonyl-brend-4-ene 1 was first attempted in the usual manner in methanol, diethyl ether or ethyl acetate as the solvent, using a Parr apparatus with a hydrogen pressure of 2.5 atm. and Pd(10% C) as the catalyst. The product isolated no longer showed the typical symmetry pattern for the brendene system in the ^{1}H-NMR spectrum indicating that again a skeletal rearrangement to the brexene system had taken place. This was confirmed by subjecting 2,9-carbonyl-brex-4-ene 5 to these hydrogenation conditions. In a smooth and clean reaction brexane 34 was obtained in almost quantitative yield. This product proved identical with the material obtained by hydrogenation of 1. It was assumed that this rearrangement is induced by the

presence of some traces of acid for which 1 is extremely sensitive (Scheme 3.17).

In order to avoid such a skeletal rearrangement the hydrogenation was performed under slightly basic conditions in the presence of a small amount of diethylamine in methyl acetate as the solvent. Indeed, under these conditions reduction of the olefinic bond proceeded smoothly without any skeletal rearrangement. The brendanone 35 was obtained in an excellent yield of 89%. The NMR- spectra clearly revealed the symmetry of the reduction product 35 (Scheme 3.17). The positions of the ^{13}C-NMR signals for the carbonyl carbon in 35 and 1 are of interest in connection with the alleged interaction between the two orthogonal π systems in 1. The observation of a lower ^{13}C-NMR signal in 1 (δ=199.6 ppm) as compared with 35 (δ=202.2 ppm) may be interpreted as an indication for π-π interaction in compound 1. In relation herewith, it is also interesting to compare the positions of the ^{13}C-NMR signals for the olefinic carbons of 1 and those for bis-olefin 32, because of the different π-π interaction for both compounds. Theoretically this interaction should be larger for 1 than for 32 because of the stronger electron-accepting character of the carbonyl function, which again should result in a higher ^{13}C-NMR signal for the olefinic carbons of 1. Comparing the resonances of the olefinic carbons of 1 and 32 indeed show this carbon in 1 to be at lower field position (δ=137.8) than that in 32 (δ=133 ppm) therefore presenting additional evidence for π-π interaction between both orthogonal unsaturated functions in 1.

Scheme 3.17 Hydrogenation of 1 with Pd



3.2.3.2 Reaction with diazomethane.

An interesting reaction involving the olefinic bond in 1 and 2 was observed with

diazomethane. Although it was originally intended to perform a ring expansion at the carbonyl unit, diazomethane was found to react exclusively with the strained olefinic bond in **1** and **2**. Even using an excess of diazomethane left the ketone function untouched. The products found were typically the result of a 1,3-cycloaddition. This 1,3-cycloaddition reaction resembles that of diazomethane with norbornene, which also undergoes a cycloaddition with diazomethane rather smoothly[13]. As has been reported by Huisgen *et al*[13] norbornene reacts twenty times faster than a comparable non-cyclic and non-strained olefin. This higher reactivity is ascribed to the relief in strain and hyperconjugative interaction between the olefin and methano bridge[14].

The relative reactivity of system **1** toward diazomethane was estimated by performing competition experiments with methyl cinnamate on one hand and with styrene on the other. It was found that **1** reacts much slower than methyl cinnamate and slightly faster than styrene. This finding implies that the olefinic bond in **1** is considerably more reactive than that in norbornene (Rate constants according to Geittner and Huisgen[13], in DMF at 25°C, norbornene: $20x10^5$ L mol^{-1} s^{-1}, styrene: $44.5x10^5$ L mol^{-1} s^{-1}, methyl cinnamate: $264x10^5$ L mol^{-1} s^{-1}). Probably, this enhanced reactivity of the olefinic bond in **1** can be attributed to the higher strain in **1** as compared with norbornene. In cycloadditions of this type diazomethane acts as the HOMO component and consequently the brendene system as the LUMO[15].

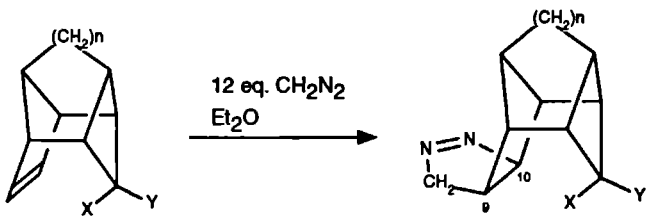
The structure of cycloadduct **36** (Scheme 3.18) could be deduced from a ^{1}H-NMR spectral analysis in which characteristic signals are present for the CH_2 unit in the pyrazoline ring and the carbon atom (C_{10}) next to the nitrogen.

The homolog 2,9-carbonyl-1,8-homo-brend-4-ene **2** reacts similarly with diazomethane to give pyrazoline **37** in a high yield of 95%(GLC)(Scheme 3.18).

To verify whether the carbonyl unit in **1** and **2** has any influence on the ability of the olefinic bond to undergo a cycloaddition reaction with diazomethane, 2,9-methano-brend-4-ene-10-*endo*-ol **22** was also subjected to a reaction with diazomethane (Scheme 3.18). It was found that the inside alcohol **22** reacted with diazomethane to pyrazoline **38** but at a considerably slower rate than the corresponding carbonyl compound. Also the acetoxy derivative of **22**, namely **24**, was brought into reaction with diazomethane. The formation of the cycloadduct **39** (Scheme 3.18) took place in a slower rate than for carbonyl brendene **1**, but faster than for *endo* carbinol brendene **22**. For the *endo* carbinol **23** and its *endo* acetate **25**, derived from carbonyl homo-brendene **2**, similar results were obtained (Scheme 3.18).

The observation of a relative fast 1,3-dipolar cycloaddition of diazomethane with ketones **1** and **2** as compared with the corresponding *endo* alcohols and their acetates shows a distinct influence of the carbonyl function on the reactivity of the olefinic function. This effect of the carbonyl function can be best explained by assuming a non-bonding interaction between the olefinic bond and the carbonyl function forming a homoconjugated enone which has a lower LUMO energy than the nonconjugated double bond as present in the endo-alcohols and acetates. The ultimate result is a faster 1,3-cycloaddition reaction for **1** and **2**. The difference in rates between the endo-alcohols **22**, **23** and their respective acetates **24**, **25** may be the effect of hydrogen bonding of the endo-hydroxy

Scheme 3.18 Reaction with CH_2N_2



reactant	reaction time	product	isolated yield
1; X,Y=O; n=1	23 h.	36	61%
22; X=OH, Y=H; n=1	48 h.	38	56%
24; X=OAc, Y=H, n=1	32 h	39	62%
2; X,Y=O; n=2	22.5 h.	37	74%
23; X=OH, Y=H; n=2	70 h.	40	67%
25; X=OAc, Y=H; n=2	47.5 h.	41	63%

function with the olefinic π-system in 22, 23 (see sections 3.2.2.2 and 3.2.2.3) which will decrease the reactivity of the double bond for cycloaddition. Such an interaction would be conceivable in the corresponding *endo* acetates, when a non-bonding interaction exists between the olefinic π-system and the electron deficient carbonyl carbon of the acetate.

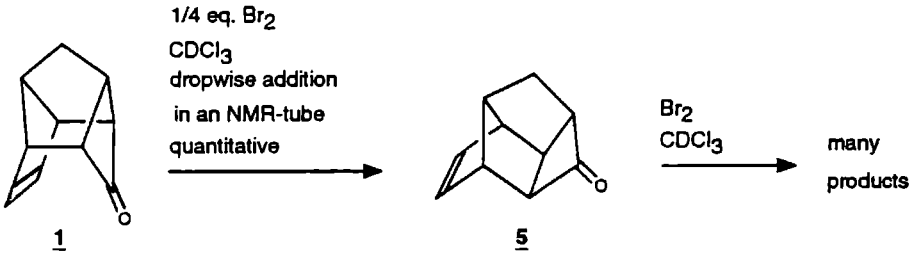
3.2.3.3 Reaction with bromine.

Electrophilic halogenation of an alkene is a well studied reaction which can give valuable information about the specific features of such an alkene function when constrained in some peculiar structure and about the chemical properties of the structure itself. For this reason the bromination of brendenones 1 and 2 was investigated.

When enone 1 was treated with bromine in chloroform at room temperature following the usual procedure, a complex mixture of products was formed from which no identifiable product could be isolated. In order to get more insight in the true nature of this bromination, this reaction of 1 with bromine was carried out by stepwise adding 0.25 equiv. of bromine and running a ^{1}H-NMR spectrum immediately after each addition. After the addition of the first batch of bromine the ^{1}H-NMR spectrum clearly showed the presence of 2,9-carbonyl-brex-4-ene 5 as the major product together with some other minor products (Scheme 3.19). The formation of 5 was unequivocally confirmed by gas chromatograhpy. Adding more bromine the product mixture got more and more

complex at the expense of 5. After the addition of one equivalent of bromine both 1 and 5 had completely disappeared to give a puzzling mixture of many products.

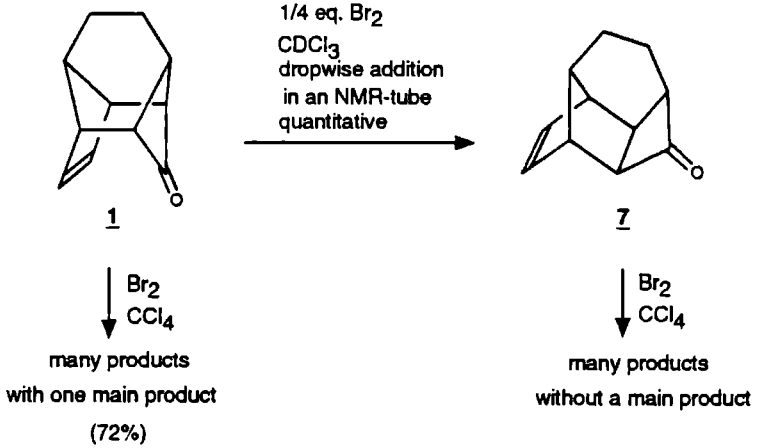
Scheme 3.19



2,9-Carbonyl-1,8-homo-brendene 2 reacted in a similar way with bromine in chloroform. After the addition of about 0.25 equiv. of bromine the only product that could be identified at that stage was again the rearranged enone, namely 2,10-carbonyl-1,9-homo-brex-4-ene 7. Both ^{1}H-NMR spectral and gas chromatographical analysis proved its formation. Further addition of bromine led again to a complex mixture of bromine containing products from which no single product could be isolated (Scheme 3.20).

An interesting result was obtained when the bromination of 2 was carried out in tetrachloormethane as the solvent. Besides some minor products one main product was now isolated in 72% yield. The structure of this product was elucidated after thorough spectral analysis.

Scheme 3.20 The reaction of 2 with bromine

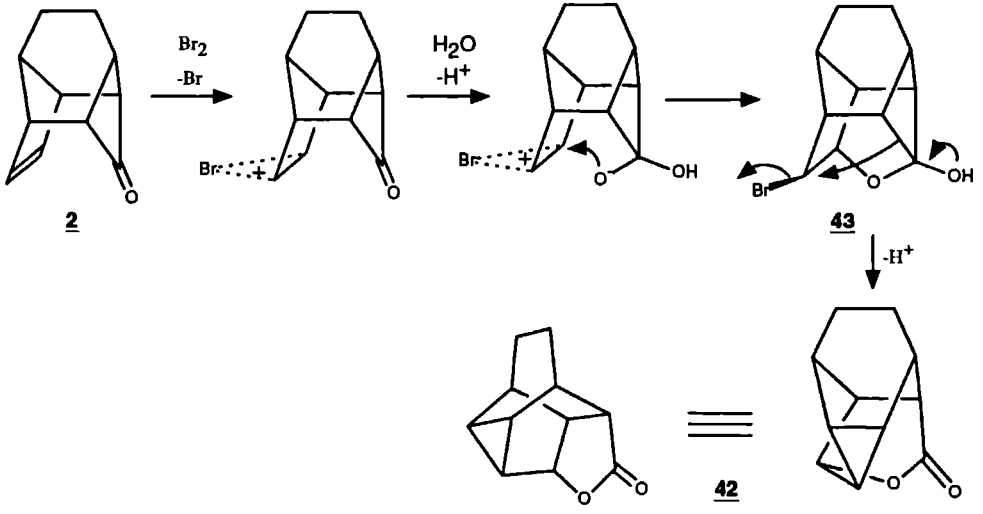


Remarkably, no bromine was present in this product. The high carbonyl absorption in the IR spectrum (1780 cm^{-1}) is indicative of a lactone unit. In the ^{13}C-NMR 11 carbon resonances were

observed, the one at 180 ppm points to a C=O and the one at 84 ppm to C-O. The ^{1}H-NMR spectrum shows only one proton in the downfield area (5.12 ppm) and a total integration value of 12 protons. From DEPT experiments (Distortionless Enhancement by Polarization Transfer) it appears that the new structure possesses one quaternary carbon atom (the carbonyl), two secondary carbon atoms (the bridge) and for the rest tertairy carbon atoms. From exact mass measurements at m/e 176 and the above findings it was concluded that the formula of the newly formed compound must be $C_{11}H_{12}O_2$, thus implying one oxygen atom more than in the starting compound 2,9-carbonyl-1,8-homo-brend-4-ene **2**. By combining all data shown above, structure **42** could be assigned to the new product.

The presence of an extra oxygen atom in this lactone **42** as compared with **2** initially presented a puzzling problem as some oxygen source is required. Its formation could however conveniently be rationalized by assuming the presence of some water in the reaction medium (Scheme 3.21). Assuming the initial formation of a bromonium ion by addition of bromine to the olefinic bond, this *exo* bromonium ion can intramolecularly be opened by trans-annular reaction with the hydrated carbonyl group, thus giving intermediate **43**. A carbonyl forming elimination reaction accompanied by an expulsion of bromide via a 1,2-shift of a C-C bond, then leads to isolated product **42**.

Scheme 3.21



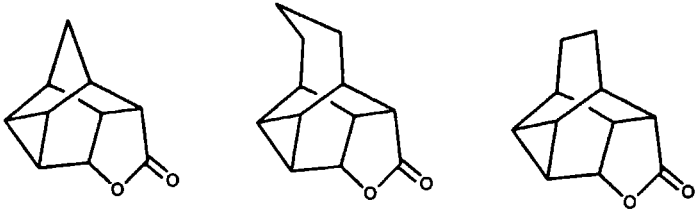
2 **43** **42**

When attempts were made to exclude the presence of water in the reaction mixture by drying and distilling both the tetrachloromethane and bromine, the yield of **42** decreased considerably and the reaction with bromine went much slower. On the other hand, when the solvent was saturated with water prior to the reaction, a much faster reaction of **2** with bromine to give **42** was observed. When N-bromosuccinimide was used as the brominating agent the same product **42** was obtained (69%,

GLC). These observations support the course of the reaction as depicted in scheme 3.20. Interestingly, treatment of brendenone 1 with bromine in tetrachloromethane and in the presence of water did not lead to any lactone. Instead initial formation of carbonyl-brexene 5 is observed which subsequently leads to a complex mixture of products. This difference in behaviour of 1 and 2 toward bromine under these conditions may be explained by the higher rigidity of 1 as compared to 2. In order to effectively open up the bromonium ion the inside oxygen anion has to move outward in order to allow effective overlap at one of carbon atoms. For 1 this leads to considerable torsion due its rigid structure whereas for 2, which, as the result of the extra methylene unit in the bridge, is somewhat more flexible, such a movement is quite feasible. Hence, for 1 the acid induced rearrangement to 5 becomes competitive and no or hardly any lactone is formed. In a final experiment carbonyl-homo-brexene 7 was also treated with bromine in tetrachloromethane, but again a complex mixture was obtained from which no single reaction product could be isolated. Thus, the formation of lactone 42 is typically associated with structure 2.

It is of interest to note that some related lactones, *viz.* 44 and 45 are reported in the literature[16,17]. In fact, the only difference is the size of the bridge. A comparison of the spectral features of 42 with those of 44 and 45 forms an additional support for the correctness of structure 42 (Scheme 3.22).

Scheme 3.22



44 45 42

IR:	44		1781 cm^{-1} (CCl_4)	
	42		1780 cm^{-1} (CCl_4)	1765 cm^{-1} ($CHCl_3$)
	45			1765 cm^{-1} ($CHCl_3$)
^{1}H-NMR ($CDCl_3$):	44		5.06(dd,1H), 3.2-1.4(m,9H)	
	42	(400 MHz)	5.12(dd,1H), 2.63(dd,1H), 2.37(m,1H)	
			2.25(m,1H), 2.19(bd,1H), 1.73-157	
			(m,5H), 1.49(m,1H), 1.17(dd,1H)	
	45		5.0(dd,1H), 2.7-1.6(m,12H), 1.25(q,1H)	

In conclusion, the bromination of both 1 and 2 in chloroform predominantly leads to initial formation of the corresponding carbonyl-brexenes 5 and 7 which then are brominated to give a

complex product mixtures. The extreme acid lability of 1 and 2 suggests that the initial rearrangement is simply a fast acid catalyzed process not involving bromine. As commercial bromine has been used in all reactions and the presence of water has been established such an acid catalyzed process is quite possible. However, these experimental results manifestly show that skeletal rearrangement effectively competes with bromination of the alkene function. This is quite surprising as the olefinic functions in 1 and 2 are rather strained and are expected to react extremely rapidly. This unexpected observation may therefore be another indication of homoconjugative interaction between the carbonyl and the olefinic functions in 1 and 2, which disfavors electrophilic substitution at the olefinic moiety. The subtility of these bromination processes is demonstrated by the deviating behavior of 2 during the bromination in tetrachlorocarbon as the solvent.

3.3 Concluding remarks

In this chapter it was shown that carbonyl-brendenes 1 and 2 are highly reactive compounds which, under influence of both Brönsted and Lewis acids, rapidly rearrange to the thermodynamically more stable carbonyl-brexenes 5 and 7. Relief of strain energy is the principal reason for this isomerization process which in essence is a cyclobutyl/cyclopropyl carbinyl rearrangement. As a result of their lability toward acidic reagents nucleophilic additions to the carbonyl function in both 1 and 2, which requires the use of some acidic catalyst or reagent, could not be accomplished. Even Grignard reagents did not give the anticipated addition at the cyclobutanone carbonyl function but they functioned primarily as Lewis acids, leading to complete isomerization. Sofar nucleophilic additions to 1 and 2 with retention of the brendene skeleton could only be achieved with organolithium compounds and lithium aluminum hydride. Attempts to produce imine derivatives of 1 and 2 under neutral or slightly basic conditions did not produce any addition product for 1 and led to a remarkable bond cleavage reaction for 2. Interestingly, the Wittig olefination using methylenetriphenylphosphorane was successful for 1 but failed completely for 2. The rather long reaction time needed for this conversion of 1 shows again the reluctance of the cyclobutanone carbonyl function to undergo nucleophilic additions. The experimental results allow the conclusion that the carbonyl function in both 1 and 2 is surprisingly inert toward nucleophilic addition. Due to relief of angle strain by going from an sp2 to sp3 carbon center nucleophilic addition to the cyclobutanone carbonyl function, is usuallly particularly favored. It may therefore be concluded that features typically associated with the structures 1 and 2 are responsible for this deviating behaviour. These features can be both of electronic and steric nature. More detailed studies will be necessary to quantify the importance of both contributions.

Some insight into the chemical reactivity of the olefinic double bond in 1 and 2 was obtained by subjecting these compounds to typical olefinic reactions such as hydrogenation, bromination and a 1,3-dipolar cycloaddition with diazomethane. Hydrogenation of the double bond in 1 without rearrangement could only be accomplished in the presence of some amine. Without amine almost

quantitive rearrangement to the carbonyl-brexene system occurred prior to hydrogenation. Bromination of both **1** and **2** in chloroform only led to complex mixtures from which no identifiable structure could be isolated. It has been demonstrated however, that rearrangement of **1** and **2** to the corresponding carbonyl-brexenes is again a major pathway. A unique cyclopropyl containing lactone was obtained in the bromination of **2** in tetrachloromethane. Such a lactone formation was not observed for **1** probably because of its lower reactivity due to its higher rigidity. Finally, diazomethane addition to **1**, **2** and their corresponding alcohols and acetates showed a distinct effect of the carbonyl function on the reactivity of the olefinic double bond in this cycloaddition. The higher reactivity of enones **1** and **2** as compared with the corresponding alcohols and acetates can be explained by assuming non-bonding interaction between the two π-functions.

3.4 Experimental Part

For general remarks, see chapter 2, section 2.4

Tetracyclo[4.4.0.0^{2,8}.0^{4,7}]dec-9-en-5-one 2,4-dinitro-phenylhydrazone (**3**)

A solution of 2,9-carbonyl-brend-4-ene **1** (150 mg, ca. 1 mmol) in methanol (ca. 1 ml) was added to a stirred filtered solution of 2,4-dinitrophenylhydrazine (0.25 g, ± 1.3 mmol) and 0.4-0.5 ml conc. sulfuric acid in MeOH (5 ml) at ca. 40 °C. The solid material which was formed after 10 min. was collected by filtration and washed with water saturated with methanol (15 ml). This gave 235 mg (70%) of **3**, which was recrystallized from ethanol, mp. 235 °C (decomposition).

IR (CCl_4) v: 2960 (C-H, unsaturated), 1335 (NO_2), 1610, 920-910 (C-H, aromatic) cm^{-1}.^{1}H-NMR ($CDCl_3$; 90MHz) δ: 10.85-10.7 (d, 1H, J = 7Hz), 9.1 (d, 1H, J=3Hz), 8.3-8.15 (dd, 1H, J = 10Hz + 3Hz), 7.85-7.7 (d, 1H, J=10Hz), 6.1 (m, 2H), 3.6-1.5 (m, 8H) ppm. EI/MS m/e: 326 (M^+, 4.5%), 135 (13.7%), 97 (15%), 84 (14.5%), 83 (23.4%), 71 (17.7%), 70 (26.3%), 69 (48.3%), 57 (72.2%). Found: C, 58.97%, H, 4.19%, N, 17.10% (Calc for $C_{16}H_{14}N_4O_4$: C, 58.89%, H, 4.32%, N, 17.17%)

Tetracyclo[4.4.0.0^{2,8}.0^{4,7}]dec-9-en-5-one (**5**)

A catalytic amount of anhydrous $AlCl_3$ was added to a stirred solution of **1** (300 mg, ± 2 mmol) in diethyl ether (25 ml). After 10 min. of stirring, water (5 ml) was added and the ethereal fraction was washed with aqueous saturated $NaHCO_3$ (5 ml), then dried ($MgSO_4$) and concentrated *in vacuo*. Product **5** was obtained as a light yellow oil (257 mg, 85%).

The same product was also obtained as follows:

A) A solution of **1** (160 mg, 1.1 mmol) in dry ether (5 ml) was added to freshly prepared methyl magnesium iodide [from Mg curlings (30 mg, ca. 1.2 mmol), MeI (250 mg, 1.75 mmol) and 2 drops of 1,2-dibromoethane] in dry ether (5 ml) at room temperature. A white precipitate appeared almost immediately. After 10 min. aqueous saturated $NaHCO_3$ (5 ml) was added, the aqueous phase was extracted with ether (25 ml) and the combined ethereal phases were washed with water. The resulting ethereal phase was dried ($MgSO_4$) and concentrated *in vacuo* to give **5** (150 mg, 1 mmol, 93%) as a light yellow oil.

B) A solution of Br_2 (55 mg, 0.34 mmol) in $CDCl_3$ (0.5 ml) was added dropwise to a solution of **1** (50 mg, 0.34 mmol) in $CDCl_3$ (0.75 ml) in a NMR-tube. After the addition of about 0.25 equiv. of Br_2 the ^{1}H-NMR spectrum of the reaction mixture showed complete conversion to compound **5**. After the addition of $CHCl_3$ (10 ml) the organic fraction was washed with a 2% aqueous $Na_2S_2O_5$ (3 ml) and water (5 ml), dried ($MgSO_4$) and concentrated *in vacuo*, to give **5** (47 mg, 0.32 mmol, 94%) as light yellow oil.

IR (CCl_4) v: 3070 (C-H, unsaturated), 2980-2880 (C-H, saturated), 1780 (C=O, 4-membered ring ketone) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 90MHz) δ: 6.1 (m, 2H), 3.3-1.7 (m, 8H) ppm. ^{13}C-NMR ($CDCl_3$; 15MHz) δ: 205 (carbonyl carbon), 136+134 (olefinic carbons), 64, 59, 57, 56, 53, 34.5, 34 ppm. EI/MS m/e: 146 (M^+, 21.3%), 118 (-CO, 12.7%), 117 (35.2%), 111 (22.1%), 97 (35.9%), 96 (23.1%),

83 (38.0%), 69 (78.1%), 55 (100.0%). EI/HRMS m/e: 146.0727 amu (Calc for $C_{10}H_{10}O$: 146.0732 amu).

Tetracyclo[5.4.0.0^{2,9}.0^{5,8}]undec-10-en-6-one (7)

In a similar way as described for 5, a catalytic amount of $AlCl_3$ was added to a stirred solution of carbonyl-homobrendene 2 (300 mg, 1.9 mmol) in dry diethyl ether (40 ml). After stirring for 10 min. water (5 ml) was added and the ethereal fraction washed with aqueous saturated $NaHCO_3$, then dried ($MgSO_4$) and concentrated *in vacuo*. Compound 7 (271 mg, 90%) was obtained with a purity of 98% (GLC). Pure 7 was obtained by flash chromatography (silica gel, n-hexane/EtOAc = 4/1).

In a similar way as described for 5, product 7 could also be obtained as follows:

A) A solution of 2 (300 mg, 1.88 mmol) in dry ether (10 ml) was added to freshly prepared methyl magnesium iodide [from Mg curlings (55 mg, 2.26 mmol), MeI (440 mg, 3.09 mmol) and 2 drops of 1,2-dibromoethane] in dry ether (10 ml) at room temperature. The reaction was followed with GC. Complete transformation into 7 was observed after 2.5 h. Then, water and a small amount of aqueous saturated NH_4Cl was added. The ethereal phase was extracted with water (2 x 5 ml) and the water fraction washed with diethyl ether (2 x 5 ml). The combined ethereal fractions were dried ($MgSO_4$) and concentrated *in vacuo*. Product 7 was obtained as a colorless oil (282 mg, 1.76 mmol, 94%).

B) A solution of Br_2 (50 mg, 0.31 mmol) in $CDCl_3$ (0.5 ml) was added dropwise to a solution of 2 (50 mg, 0.31 mmol) in $CDCl_3$ (0.75 ml) in a NMR-tube. After the addition of about 1/4 equiv. of Br_2 the ^{1}H-NMR spectrum of the reaction mixture showed complete conversion to 7. After addition of $CHCl_3$ (10 ml) the organic fraction was washed with a 2% aqueous $Na_2S_2O_5$ solution (3 ml) and water (5 ml), dried ($MgSO_4$) and concentrated *in vacuo*, to give 7 (43 mg, 0.27 mmol, 86%) as light yellow oil.

IR (CCl_4 or KBr) ν: 1770 (s, C=O, 4-membered ring ketone) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 6.22 (dd, 1H), 6.13 (dd, 1H), 3.07 (m, 1H), 2.94 (d, 1H), 2.91 (dd, 1H), 2.70 (bs, 1H), 2.47 (dt, 1H), 2.04 (bd, 1H), 1.86 (m, 1H), 1.35-1.48 (m, 2H), 1.27 (m, 1H) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 213 (quat, carbonyl), 139 (tert, olefine), 137 (tert, olefine), 66 (tert), 52 (tert), 51 (tert), 48 (tert), 41 (tert), 32 (tert), 23 (sec, bridge), 15 (sec, bridge) ppm. EI/MS m/e: 160 (M^+, 19%), 131 (-CO / -C_2H_2, -H^+, 33%), 117 (-C_2H_2, -OH, 93%), 116 (-C_2H_2, -H_2O, 100%), 104 (-C_2H_2, -CO, 38%), 91 (54%). EI/HRMS m/e: 160.0895 amu (Calc for $C_{11}H_{12}O$: 160.0888 amu).

10-exo-Chloro-tricyclo[5.2.1.0^{4,8}]dec-5-en-2-one (8)

Concentrated HCl 36% aq. (10 ml) was added to a stirred solution of 1 (100 mg, 0.68 mmol) in EtOH (10 ml). After 10 min. the mixture was diluted with water and extracted with $CHCl_3$ (3 × 30 ml). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*, to give 8 (121 mg, 0.66 mmol) as a white solid in a yield of 96%. Recrystallisation from n-hexane, gave pure 8 as white crystals (m.p. 39°C).

IR (CCl_4) ν: 3060 (s, -CH unsat.), 2960 + 2920 + 2900 (s, -CH sat.), 1720 (s, -C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 90MHz) δ: 5.85 (dd, 1H, olefine), 5.65 (dd, 1H, olefine), 3.7 (s, 1H, -CHCl), 3.2-2.0 (m,

8H) ppm. EI/MS m/e: 184 ($M^+(^{37}Cl)$, 10.4%), 182 ($M^+(^{35}Cl)$, 32.0%), 147 (-Cl, 17.2%), 119 (-Cl, -C=O, 14.5%), 105 (-Cl, -C=O, $-CH_2$, 100.0%), 91 (17.9%), 79 (21.3%). EI/HRMS m/e: 182.0498 amu (Calc for $C_{10}H_{11}OCl$: 182.0498 amu). Found: C, 65.82%, H, 6.12% (Calc for $C_{10}H_{11}OCl$: C, 65.76%, H, 6.07%, O, 8.76%, Cl, 19.41%).

10-exo-*Bromo-tricyclo[5.2.1.0^{4,8}]dec-5-en-2-one* (**9**)

Compound **9** was prepared as described for **8**, using **1** (300 mg, 2.05 mmol) in MeOH (30 ml) and concentrated HBr 48% aq. (30 ml). After 10 min. the mixture was diluted with water and extracted with $CHCl_3$ (3 × 30 ml). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*, to give **9** (200 mg, 0.88 mmol, 43%) as a white solid. Recrystallisation from n-hexane, gave **9** as white crystals (m.p. 33.5°C).

IR (CCl_4) ν: 3060 (s, -CH unsat.), 2960 + 2920 + 2890 (s, -CH sat.), 1720 (s, -C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 90MHz) δ: 5.9 (dd, 1H, olefine), 5.6 (dd, 1H, olefine), 3.8 (bs, 1H, -CHBr), 3.5-2.0 (m, 8H) ppm. EI/MS m/e: 228 ($M^+(^{81}Br)$, 5.72%), 226 ($M^+(^{79}Br)$, 5.98%), 147 (-Br, 54.0%), 105 (-Br, -C=O, $-CH_2$, 100.0%), 91 (8.61%), 79 (9.74%). EI/HRMS m/e: 225.9994 amu (Calc for $C_{10}H_{11}OBr$: 225.9993 amu). Found: C, 53.45%, H, 4.95% (Calc for $C_{10}H_{11}OBr$: C, 52.89%, H, 4.88%, O, 7.05%, Br, 35.8%).

11-exo-*Bromo-tricyclo[5.3.1.0^{4,8}]undec-5-en-2-one* (**10**)

Compound **2** (300 mg, 1.9 mmol) was dissolved in a 1:1 mixture of conc. HBr 48% aq. and methanol (25 ml). After stirring for 72 h at r.t. the reaction mixture was extracted with diethyl ether (1 × 35 ml and 2 × 20 ml). The combined ethereal fractions were washed with water (1 × 10 ml and 2 × 5 ml), dried ($MgSO_4$) and concentrated *in vacuo*, to give crude **10** as a brown oil (355 mg). Purification applying flash chromatography (silica gel, n-hexane/EtOAc=5/1), yielded **10** (252 mg, 1.06 mmol, 56%) as a colorless oil.

IR (CCl_4) ν: 1708 (carbonyl) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 5.83 (dd, 1H), 5.73 (dt, 1H), 4.07 (dd, 1H), 3.23 (dt, 1H), 3.05 (dd, 1H), 2.76 (m, 1H), 2.73 (tt, 1H), 2.65 (m, 1H), 2.36 (tdd, 1H), 2.27 (dm, 1H), 2.23 (m, 1H), 2.05 (tm, 1H), 1.93 (m, 1H) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 211 (quat, carbonyl), 136 (tert, olefine), 134 (tert, olefine), 54 (tert), 52 (tert), 49 (tert), 46 (sec), 44 (tert), 38 (tert), 19 (sec, bridge), 17 (sec, bridge) ppm. EI/GCMS m/e: 242 (M^+, 46%), 161 (-Br, 100%), 143 ($-H_2O$, -Br, 20%), 133 (-Br, $-C_2H_2$/-CO, 47%), 119 (-Br, $-C_2H_2$, -O,99%), 117 (-Br, $-C_2H_4$, -O,41%), 115 (15%), 91 (65%), 79 (11%), 65 (5%). EI/HRMS m/e: 240.0152 amu (Calc for $C_{11}H_{13}OBr$: 240.0150.)

11-Methoxy-tricyclo[5.3.1.0^{4,8}]dec-5-en-2-one (**11**)

Ketone **2** (300 mg, 1.9 mmol) was dissolved in a 3:1 mixture of respectively methanol and conc. sulfuric acid (25 ml). After stirring for 72 h at r.t. the reaction mixture was extracted with diethyl ether (2 × 25 ml and 1 × 10 ml). The combined ethereal fractions were washed with water (3 × 5 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product **11** (160 mg, 44%) as a dark

yellow oil (purity of 70%). Purification applying flash chromatography (silica gel, n-hexane/EtOAc = 4/1) gave pure **11** but in poor yield.

IR (CCl_4) ν: 1702 (s, carbonyl), 1095 (s, C-O) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 5.78 (dd, 1H), 5.71 (dt, 1H), 3.30 (s, 3H, -OMe), 3.05 (bs, 1H), 3.04 (dd, 1H), 2.77 (m, 2H), 2.66 (dt, 1H), 2.60 (m, 1H), 2.26 (dm, 1H), 2.15-1.85 (m, 3H), 1.76 (m, 1H) ppm. ^{13}C-NMR ($CDCL_3$, 100MHz) δ: 213 (quat, carbonyl), 136 (tert, olefine), 134 (tert, olefine), 76 (tert, C-OMe), 56 (prim, OMe), 49 (tert), 48 (tert), 46 (sec), 44 (tert), 38 (tert), 18 (sec, bridge), 17 (sec, bridge) ppm. EI/GCMS m/e: 192 (M^+, 94%), 177 (-CH_3, 3%), 160 (-MeOH, 21%), 150 (-CH_2CO, 11%), 132 (-CO, -MeOH, 17%), 118 (30%), 91 (29%), 84 (100%), 77 (17%), 71 (87%). EI/HRMS m/e: 192.1146 amu (Calc for $C_{12}H_{16}O_2$: 192.1150 amu).

5-Hydroxy-5-methyl-tetracyclo[4.4.0.0^{2,8}.0^{4,7}]dec-9-ene (**14**)

Compound **14** was prepared as described for **5**, using **1** (160 mg, 1.1 mmol) in dry ether (5 ml) and freshly prepared methyl magnesium iodide [from Mg curlings (30 mg, ± 1.2 mmol), MeI (250 mg, 1.75 mmol) and 2 drops of 1,2-dibromoethane], but now in refluxing dry ether (5 ml). After stirring for 30 min under reflux, the reaction mixture was allowed to cool to r.t. Then, water (5 ml) was added and the ethereal fraction was washed with aqueous saturated $NaHCO_3$ (5 ml), dried ($MgSO_4$) and concentrated *in vacuo*, which resulted in a yellow oil (150 mg) consisting of **5** (18%) and **14** (75%) (GC). Purification of **14** was realized applying flash chromatography (silica gel; n-hexane/EtOAc = 4/1) to give **14** (106 mg, 0.65 mmol, 60%) as a colorless oil.

IR (CCl_4) ν: 3600 (m, -OH) + 3350 (s, -OH), 3055 (m, -CH unsat.), 2940 + 2880 (s, -CH sat.) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 5.98 (dd, 1H, olefine), 5.86 (dd, 1H, olefine), 2.84 (bs, 1H), 2.67 (d, 1H), 2.43 (dt, 1H), 2.16 (bs, 1H), 2.03 (m, 1H), 1.87 (s, 1H), 1.84 (s, 1H), 1.69 (t, 1H), 1.65 (bs, 1H, -OH), 1.59 (dt, 1H), 1.40 (s, 3H, -Me) ppm. EI/MS m/e: 162 (M^+, 17.2%), 147 (-CH_3, 20.4%), 119 (-C=O, -CH_3, 24.1%), 104 (20.0%), 91 (27.7%), 79 (15.3%). EI/HRMS m/e: 162.1046 amu (Calc for $C_{11}H_{14}O$: 162.1045 amu).

6-endo-*Hydroxy-6*-exo-*methyl-tetracyclo[5.4.0.0^{2,9}.0^{5,8}]undec-10-ene* (**15**)

A solution of **2** (150 mg, 0.94 mmol) in dry THF (5 ml) was added to freshly prepared methyl magnesium iodide [from Mg curlings (60 mg, 2.5 mmol), MeI (500 mg, 3.5 mmol)] in dry THF (10 ml) heated to reflux. After 30 h. an optimal yield of **15** (73% GC) was obtained. Then, diethyl ether (40 ml) and an aqueous saturated NH_4Cl solution (10 ml) were added. The combined organic fraction were extracted with water (2 × 5 ml), dried ($MgSO_4$) and concentration *in vacuo*, to give crude product **15** as a brown oil. Purification by flash chromatography (silica gel, n-hexane/EtOAc = 4/1), gave **15** (85 mg, 0.48 mmol, 52%) as a white solid (m.p. 68°C).

IR (KI) ν: 3615 (s, -OH) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 6.14 (dd, 1H, olefine), 5.92 (dd, 1H, olefine), 2.64 (bs, 2H), 2.21 (dt, 1H), 1.90-1.75 (m, 5H), 1.47-1.38 (m, 2H), 1.45 (s, 3H, -Me) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 139 (tert, olefine), 135 (tert, olefine), 70 (quat, -C(OH)Me), 52 (tert), 51 (tert), 46 (tert), 41 (tert), 40 (tert), 32 (tert), 31 (prim, -Me), 24 (sec, bridge), 17 (sec,

bridge) ppm. EI/MS m/e: 176 (M^+, 24%), 161 (-Me, 3%), 158 (-H_2O, 5%), 143 (-Me, -H_2O, 7%), 133 (-C_2H_2, -OH, 22%), 118 (-OH, -C_2H_2, -Me, 100%), 91 (47%), 84 (17%), 79 (24%), 43 (63%). EI/HRMS m/e: 176.1193 amu (Calc for $C_{12}H_{16}O$: 176.1205 amu). Found: C, 81.64%, H, 9.11% (Calc for $C_{12}H_{16}O$: C, 81.77%, H, 9.15%).

3-endo-*Hydroxy-3*-exo-*methyl-tetracyclo[5.3.0.0^{2,5}.0^{4,8}]dec-9-ene* (**16**)

MeLi (1.6 mmol, 1 ml of a 1.6 M solution in n-hexane) was added to a solution of **1** (150 mg, 1.03 mmol) in dry diethyl ether (10 ml) with a syringe at -78°C under an N_2-atm. After stirring for 1 h., the mixture was allowed to attain r.t. Then, the mixture was quenched with diethyl ether (30 ml) and water (10 ml). The ethereal fraction was washed with water (2 x 10 ml), dried ($MgSO_4$) and concentrated *in vacuo*, to give **16** (125 mg, 0.77 mmol, 75%) as a yellow oil.

IR (CCl_4) v: 3580 (-OH) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 6.52 (t, 2H, olefine), 5.16 (d, -OH), 2.97 (m, 1H), 2.67 (m, 3H), 2.56 (m, 2H), 1.52 (s, 2H, bridge), 1.3 (d, 3H, -Me) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 141.25 (tert, 2C, olefine), 76.21 (quat, 1C, -C(H)OH), 67.27 (tert, 1C), 53.48 (tert, 2C), 50.14 (tert, 2C), 46.83 (tert, 1C), 32.32 (sec, 1C, bridge), 29.68 (prim, -CH_3) ppm. EI/MS m/e: 162 (M^+, 9.95%), 147 (-CH_3, 17.29%), 129 (-CH_3, -H_2O, 15.06%), 119 (-CH_3CO, 57.47%), 104 (90.23%), 91 (52.94%), 79 (31.11%). EI/HRMS m/e: 162.1045 amu (Calc for $C_{11}H_{14}O$: 162.1045 amu).

7-endo-*Hydroxy-7*-exo-*methyl-tetracyclo[5.4.0.0^{2,9}.0^{5,8}]undec-10-ene* (**17**)

Compound **17** was prepared as described for **16**, using MeLi (2.0 mmol, 1.25 ml of a 1.6 M solution in n-hexane), **2** (80 mg, 0.5 mmol) in dry diethyl ether (10 ml). After stirring for 1 h., the mixture was allowed to attain r.t. Then, the mixture was quenched with diethyl ether (30 ml) and water (10 ml). The ethereal fraction was washed with water (2 x 10 ml), dried ($MgSO_4$) and concentrated *in vacuo*, to give **17** (80 mg, 0.45 mmol, 91%) as a white solid (m.p. 42°C).

IR (CCl_4) v: 3585 (s, -OH) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 6.86 (t, 2H, olefine), 5.33 (d, 1H, -OH), 2.62 (m, 2H), 2.51 (td, 2H), 2.26 (m, 1H), 2.13 (m, 1H), 1.71 (s, 3H, -CH_3), 1.53 (s, 2H, bridge) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 146.2 (tert, 2C, olefine), 79.4 (quat, 1C), 54.6 (tert, 1C), 52.2 (tert, 2C), 44.9 (tert, 2C), 34.0 (tert, 1C), 31.4 (prim, 1C, -CH_3), 21.4 (sec, 1C), 16.9 (sec, 1C) ppm. CI/MS m/e: 177 (M^++1, 1.4%), 176 (M^+, 5.2%), 175 (-H_2, 5.4%), 159 (-H^+, -H_2O, 66%), 133 (14%), 131 (11%). EI/HRMS m/e: 176.1218 amu (Calc for $C_{12}H_{16}O$: 176.1212 amu).

3-endo-*Hydroxy-3*-exo-*n-butyl-tetracyclo[5.3.0.0^{2,5}.0^{4,8}]dec-9-ene* (**18**)

Compound **18** was prepared as described for **16**, using n-BuLi (3.2 mmol, 2 ml of a 1.6 M solution in n-hexane), **1** (150 mg, ± 1.0 mmol) in dry diethyl ether (10 ml). After stirring for 1 h., the mixture was allowed to attain r.t. Then, the mixture was quenched with diethyl ether (30 ml) and water (10 ml). The ethereal fraction was washed with water (2 x 10 ml), dried ($MgSO_4$) and concentrated *in vacuo*, to give **18** (180 mg, 0.88 mmol, 86%) as a colorless oil.

IR (CCl_4) v: 3580 (-OH) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 6.51 (t, 2H, olefine), 5.10 (bs, 1H,

-OH), 2.98 (m, 1H), 2.68 (m, 2H), 2.65 (m, 1H), 2.59 (m, 2H), 1.63 (t, 2H, $-CH_2$), 1.51 (s, 2H, bridge), 1.37 (m, 2H, $-CH_2$), 1.28 (q, 2H, $-CH_2$), 0.89 (t, 3H, $-CH_3$) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 141.37 (tert, 2C, olefine), 78.4 (quat, 1C, $-C(OH)(CH_2)_3CH_3$), 67.57 (tert, 1C), 51.87 (tert, 2C), 50.20 (tert, 2C), 46.55 (tert, 1C), 41.49 (sec, 1C), 32.41 (sec, 1C, bridge), 25.68 (sec, 1C), 23.14 (sec, 1C), 14.11 (prim, 1C, $-CH_3$) ppm. EI/MS m/e: 204 (M^+, 17.11%), 187 (-OH, 7.19%), 147 ($-C_4H_9$, 85.43%), 129 ($-C_4H_9$, -CO, 38.70%), 119 (67.0%), 104 (100.0%), 91 (92.54%), 85 (57.63%), 79 (46.26%). EI/HRMS m/e: 204.1511 amu (Calc for $C_{14}H_{20}O$: 204.1514 amu).

7-endo-*Hydroxy-7*-exo-*n-butyl-tetracyclo[5.4.0.0^{2,9}.0^{5,8}]undec-10-ene* (**19**)

Compound **19** was prepared as described for **16**, using n-BuLi (1.6 mmol, 1 ml of a 1.6 M solution in n-hexane), **2** (200 mg, ± 1.25 mmol) in dry diethyl ether (10 ml). After stirring for 1 h., the mixture was allowed to attain r.t. Then, the mixture was quenched with diethyl ether (30 ml) and water (10 ml). The ethereal fraction was washed with water (2 x 10 ml), dried ($MgSO_4$) and concentrated *in vacuo*, to give **19** (264 mg, 1.21 mmol, 97%) as colorless crystals (m.p. 30°C).

IR (CCl_4) ν: 3580 (s, -OH) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 6.85 (t, 2H, olefine), 5.24 (s, 1H, -OH), 2.63 (m, 2H), 2.53 (m, 2H), 2.33 (m, 2H), 1.70 (m, 6H), 1.40 (m, 2H), 1.30 (m, 2H) 0.90 (t, 3H, -Me) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 146.2 (tert, 2C, olefine), 81.8 (quat, 1C, -C(OH)n-Bu), 55.0 (tert, 1C), 50.0 (tert, 2C), 44.9 (tert, 2C), 42.6 (sec, 1C), 33.3 (tert, 1C), 26.9 (sec, 1C), 23.1 (sec, 1C), 21.5 (sec, 1C), 17.0 (sec, 1C), 14.1 (prim, 1C, -Me) ppm. CI/MS m/e: 219 (M^++1, 5.3%), 218 ($-H^+$, 10.4%), 217 ($-H_2$, 14.6%), 201 ($-H^+$, $-H_2O$, 80%), 161 (-nBu, 38%). EI/HRMS m/e: 218.1666 amu (Calc for $C_{15}H_{22}O$: 218.1671 amu).

3-endo-*Hydroxy-3*-exo-*phenyltetracyclo[5.3.0.0^{2,5}.0^{4,8}]dec-9-ene* (**20**)

Compound **20** was prepared as described for **16**, using C_6H_5Li (2.0 mmol, 1 ml of a 2 M solution in benzene), **1** (150 mg, 1.03 mmol) in dry diethyl ether (10 ml) at 0°C. After stirring for 1 h., the mixture was allowed to attain r.t. Then, the mixture was quenched with diethyl ether (30 ml) and water (10 ml). The ethereal fraction was washed with water (2 x 10 ml), dried ($MgSO_4$) and concentrated *in vacuo*, to give **20** (205 mg, 0.92 mmol, 89%) as a colorless oil.

IR (CCl_4) ν: 3560 (-OH) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 7.49 (dt, 2H, arom.), 7.33 (td, 2H, arom.), 7.24 (td, 1H, arom.), 6.64 (t, 2H, olefine), 5.28 (s, 1H, -OH), 3.13 (m, 2H), 3.10 (m, 1H), 2.85 (m, 2H), 2.33 (m, 1H), 1.54 (s, 2H, bridge) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 141.15 (tert, 2C, olefine), 128.10 (tert, 2C, arom.), 126.71 (tert, 1C, arom.), 125.55 (tert, 2C, arom.), 79.03 (quat, 1C, $-C(OH)C_6H_5$), 67.94 (tert, 1C), 51.14 (tert, 2C), 50.09 (tert, 2C), 45.84 (tert, 1C), 32.68 (sec, 1C, bridge) ppm. EI/MS m/e: 224 (M^+, 8.96%), 206 ($-H_2O$, 4.35%), 191 (3.2%), 183 (4.93%), 167 (7.82%), 165 (7.82%), 158 (80.94%), 105 (100.00%), 91 (28.39%), 77 (64.63%). EI/HRMS m/e: 224.1200 amu (Calc for $C_{16}H_{16}O$: 224.1201 amu).

7-endo-*Hydroxy-7*-exo-*phenyltetracyclo[5.4.0.0^{2,9}.0^{5,8}]undec-10-ene* (**21**)

Compound **21** was prepared as described for **16**, using C_6H_5Li (1.4 mmol, 0.7 ml of a 2 M solution

in benzene), **2** (160 mg, 1 mmol) in dry diethyl ether (10 ml) at 0°C. After stirring for 1 h., the mixture was allowed to attain r.t. Then, the mixture was quenched with diethyl ether (30 ml) and water (10 ml). The ethereal fraction was washed with water (2 x 10 ml), dried ($MgSO_4$) and concentrated *in vacuo*, to give **21** (220 mg, 0.92 mmol, 92%) as white crystals (purity 93% (GC)).
IR (CCl_4) ν: 3560 (s, -OH), 700 (s, arom) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 7.43 (m, 2H, arom), 7.33 (t, 2H, arom), 7.21 (t, 1H, arom), 6.93 (t, 2H, olefine), 5.35 (s, 1H, -OH), 3.12 (m, 2H), 2.79 (m, 2H), 2.24 (m, 1H), 1.85 (m, 1H), 1.74 (m, 2H), 1.58 (m, 2H) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 145.8 (tert, 2C, olefine), 128.3 (tert, 2C, arom), 126.9 (tert, 1C, arom), 124.3 (tert, 2C, arom), 82.9 (quat, 1C, -C(OH)C_6H_5), 54.5 (tert, 1C), 48.5 (tert, 2C), 44.4 (tert, 2C), 34.6 (tert, 1C), 21.0 (sec, 1C), 16.3 (sec, 1C) ppm. CI/MS m/e: 239 (M^++1, 8.8%), 238 (-H^+, 13.4%), 237 (-H_2, 10.0%), 221 (-H^+, -H_2O, 79%), 158 (70%), 143 (-H^+, -H_2O, -C_6H_5, 23.6%), 117 (84%), 91 (100%). EI/HRMS m/e: 238.1351 amu (Calc for $C_{17}H_{18}O$: 238.1358 amu).

3-endo-Hydroxy-tetracyclo[5.3.0.0^{2,5}.0^{4,8}]dec-9-ene (**22**)
A solution of **1** (200 mg, 1.35 mmol) in diethyl ether (10 ml) was added to a suspension of $LiAlH_4$ (50 mg, 1.3 mmol) in dry diethyl ether 25 ml). After 30 min. stirring at r.t., the reaction mixture was quenched with diethyl ether (50 ml) and water (5 ml). Then, the mixture was neutralized with diluted HCl 3% aq. The isolated ethereal phase was washed with water (2 × 5 ml), dried ($MgSO_4$) and concentrated *in vacuo*, to give **22** (160 mg, 1.08 mmol, 80%) as a light yellow oil, which partially solidified in the freezer.
IR (CCl_4) ν: 3598 (s, -OH) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 6.47 (s, 2H, olefine), 4.12 (s, 1H, -OH), 4.10 (m, 1H, -C(H)OH), 3.05 (m, 1H), 2.66 (m, 2H), 2.56 (m, 2H), 2.42 (m, 2H), 1.65 (s, 2H, bridge) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 140.25 (tert, 2C, olefine), 72.02 (tert, 1C, -C(H)OH), 67.25 (tert, 1C), 49.16 (tert, 2C), 48.63 (tert, 2C), 44.54 (tert, 1C), 33.18 (sec, 1C, bridge) ppm. EI/MS m/e: 148 (M^+, 1.34%), 131 (-OH, 1.24%), 130 (-H_2O, 1.52%), 129 (1.5%), 117 (-C_2H_5/-CHO, 1.83%), 104 (2.83%), 84 (12.6%), 74 (31.28%). EI/HRMS m/e: 148.0883 amu (Calc for $C_{10}H_{12}O$: 148.0888 amu).

7-endo-Hydroxy-tetracyclo[5.4.0.0^{2,9}.0^{5,8}]undec-10-ene (**23**)
A solution of **2** (500 mg, 3.125 mmol) in diethyl ether (10 ml) was added to a suspension of $LiAlH_4$ (50 mg, 1.3 mmol) in dry diethyl ether (20 ml). After 45 min. stirring at r.t., the reaction mixture was quenched with water (5 ml). Subsequently, the mixture was neutralized with diluted HCl 3% aq. The ethereal phase was washed with water (3 × 5 ml) and the combined water phase extracted with diethyl ether (1 × 10 ml). Then, the combined ether fractions were dried ($MgSO_4$) and concentrated *in vacuo*, to give **23** (470 mg, 2.90 mmol, 93%) as a colorless oil, which partially solidified in the freezer.
IR (CCl_4) ν: 3595 (s, -OH) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 6.81 (t, 2H, olefine), 3.91 (s, 1H, -OH), 2.54 (m, 4H), 2.20 (s, 1H), 1.75 (m, 4H), 1.68 (m, 2H) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 145 (tert, 2C, olefine), 77 (tert, 1C), 54 (tert, 1C), 46.5 (tert, 2C), 43 (tert, 2C), 35 (tert, 1C), 21 (sec,

1C), 16 (sec, 1C) ppm. CI/MS m/e: 163 (M^++1, 2.2%), 162 (M^+, 14.1%), 145 (-H^+, -H_2O, 100%), 131 (18%), 117 (60%), 91 (95%). EI/HRMS m/e: 162.1049 amu (Calc for $C_{11}H_{14}O$: 162.1044 amu).

3-endo-Acetoxy-tetracyclo[5.3.0.0^{2,5}.0^{4,8}]dec-9-ene (**24**)

Ac_2O (620 mg, 6.08 mmol), Et_3N (640 mg, 6.34 mmol) and a catalytic amount of DMAP (3 crystals) was added to a solution of **1** (290 mg, 1.99 mmol) in CH_2Cl_2 (20 ml). After stirring for 24 h. CH_2Cl_2 (20 ml) was added and the mixture washed with respectively aqueous saturated NH_4Cl (1 × 5 ml), aqueous saturated $NaHCO_3$ (1 × 5 ml) and water (2 × 5 ml). Then, the organic fraction was dried ($MgSO_4$) and concentrated *in vacuo* at 40°C, to give **24** (373 mg, 1.96 mmol, 95%) as a clear, colorless oil.

IR (CCl_4) v: 1730 (s, -C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 90MHz) δ: 6.0 (s, 2H, olefine), 4.7 (t, 1H, >C**H**OAc), 2.9 (m, 1H), 2.8-2.35 (m, 5H), 1.8 (s, 3H, -C**H**$_3$), 1.6 (s, 2H, bridge) ppm. EI/MS m/e: 190 (M^+, 7.58%), 148 (-C(O)CH_2, 46.68%), 130 (-OC(O)CH_3, 100.00%), 115 (41.09%), 104 (32.33%), 91 (78.86%), 79 (34.81%), 70 (68.87%). EI/HRMS m/e: 190.0993 amu (Calc for $C_{12}H_{14}O_2$: 190.0994 amu).

7-endo-Acetoxy-tetracyclo[5.4.0.0^{2,9}.0^{5,8}]undec-10-ene (**25**)

Compound **25** was prepared as described for **24**, using Ac_2O (620 mg, 6.08 mmol), Et_3N (640 mg, 6.34 mmol), a catalytic amount of DMAP (3 crystals) and **2** (320 mg, 2 mmol) in CH_2Cl_2 (20 ml). After stirring for 48 h. CH_2Cl_2 (20 ml) was added and the mixture washed with respectively aqueous saturated NH_4Cl (1 × 5 ml), aqueous saturated $NaHCO_3$ (1 × 5 ml) and water (2 × 5 ml). Then, the organic fraction was dried ($MgSO_4$) and concentrated *in vacuo* at 40°C, to give **25** (376 mg, 1.84 mmol, 92%) as a clear, colorless oil.

IR (CCl_4) v: 1730 (s, -C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 6.34 (t, 2H), 4.55 (m, 1H, -C(**H**)OAc), 2.67 (m, 2H), 2.44 (m, 2H), 2.14 (bs, 1H), 1.98 (s, 3H, -Me), 1.92 (m, 1H), 1.78 (bs, 4H, bridge) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 171 (quat, 1C, carbonyl), 141 (tert, 2C, olefine), 76 (tert, 1C, -**C**(H)OAc), 52 (tert, 1C), 44 (tert, 2C), 42 (tert, 2C), 37 (tert, 1C), 22 (prim, 1C, -CH_3), 21 (sec, 1C, bridge), 16 (sec, 1C, bridge) ppm. EI/MS m/e: 204 (M^+, 2%), 176 (-C_2H_4, 1%), 162 (-C(O)CH_3, 27%), 144 (39%), 129 (33%), 117 (28%), 91 (52%), 43 (100%). EI/HRMS m/e: 204.1150 amu (Calc for $C_{13}H_{16}O_2$: 204.1150 amu).

5-exo-Hydroxy-tetracyclo[4.4.0.0^{2,8}.0^{4,7}]dec-9-ene (**27**)

(i-PrO)$_3$Al in i-PrOH (9 mmol, 9 ml of 1 M solution) was added to a solution of **1** (444 mg, 3.04 mmol) in dry i-PrOH (10 ml). After heating at reflux for 92 h. the mixture was allowed to attain r.t. Then, the mixture was concentrated *in vacuo*, to give a brown residue. This was dissolved in diethyl ether and neutralized with diluted HCl 3% aq. The ethereal fraction was washed with water (5 ml), dried ($MgSO_4$) and concentrated *in vacuo*, to give **27** (390 mg, 2.64 mmol, 87%) as a clear and colorless oil, which solidified upon standing. Recrystallization in n-hexane afforded pure **27** as white crystals (m.p. 64-65 °C).

IR (CCl_4) v: 3300 (s, -OH), 3050 (m, -CH unsat.), 2990 + 2940 + 2860 (m, -CH sat.) cm^{-1}. ^{1}H-NMR (CCl_4; 90MHz) δ: 5.9 (m, 2H, olefine), 4.2 (t, 1H, -CHOH), 2.9 (bs, 2H, also -OH), 2.65 (m, 2H), 2.15 (bs, 1H), 1.9 (m, 2H), 1.4 (m, 1H) ppm. EI/MS m/e: 148 (M^+, 9.6%), 130 (-H_2O, 7.5%), 117 (11.3%), 104 (11.0%), 91 (26.2%), 79 (17.7%). EI/HRMS m/e: 148.0884 amu (Calc for $C_{10}H_{12}O$: 148.0888 amu).

3-exo-Hydroxy-tricyclo[5.3.0.0^{2,5}]dec-9-ene (**28**)

1 (150 mg, 1.03 mmol) was added to a solution of Li (23 mg, 3.28 mmol) in NH_3 liq. (100 ml). After stirring for 1 h., diethyl ether (50 ml) was added. The mixture was allowed to attain r.t. and water (20 ml) was added. Subsequently, the water fraction was washed with Et_2O (20 ml). The combined ethereal fractions were dried ($MgSO_4$) and concentrated *in vacuo*, to give **28** (137 mg, 0.91 mmol, 89%) as a colorless oil (purity 80%). Further purification could be realized using flash chromatography (silica gel; n-hexane/EtOAc = 5/1), to give **28** (97 mg, 0.65 mmol) in a yield of 63% and a purity of 96%.

IR (CCl_4) v: 3620 (m) + 3320 (s, -OH), 3060 (s, -CH unsat.), 2940 + 2860 (-CH sat.) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 5.65 (m, 2H, olefine), 4.19 (q, 1H, -CHOH), 3.22 (tt, 1H), 2.76 (qt, 1H), 2.64 (m, 2H, also -OH), 2.44 (m, 2H), 2.16 (td, 1H), 2.10 (d, 1H), 2.00 (dd, 1H), 1.90 (dt, 1H), 1.02 (m, 1H) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 131.5 (tert, olefine), 129.5 (tert, olefine), 68.5 (tert, -CHOH), 54.6 (tert), 54.0 (tert), 47.2 (tert), 40.7 (sec), 38.1 (sec), 35.3 (sec), 33.3 (tert) ppm. EI/MS m/e: 150 (M^+, 3.0%), 132 (-H_2O, 1.8%), 119 (-CH_2, -OH, 4.0%), 106 (-CH_2-CHOH, 78.1%), 91 (43.3%), 78 (26.6%). EI/HRMS m/e: 150.1047 amu (Calc for $C_{10}H_{14}O$: 150.1045 amu).

6-(Bicyclo[4.3.0]nona-3,8-dienyl)-acetic acid hydrazide (**29**)

Compound **2** (160 mg, 1 mmol) was added to a mixture of hydrazine (100%, 5 ml), ethanol (5 ml) and a small amount of Na_2SO_4. The reaction mixture was heated (T=110°C) for about 53 h. under an N_2-atm. After allowing the reaction-mixture to attain r.t., filtration and concentration *in vacuo*, **29** was isolated as a brown-white powder. After recrystallization in n-hexane **29** (233 mg, 1.23 mmol, 49%) was obtained as a white powder (m.p. 76-77°C).

IR (KBr) v: 3310 (s, N-H), 1680-1640 (s, C=O amide), 1525 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 6.85 (bs, 1H, -NH), 5.80 (t, 2H, olefine), 5.65 (m, 1H, olefine), 5.50 (m, 1H, olefine), 3.95 (bs, 2H, -NH_2), 3.32 (m, 1H), 3.17 (m, 1H), 2.48 (m, 1H), 2.32 (dd, 1H), 2.22 (dd, 1H), 1.94 (m, 2H), 1.40 (m, 1H), 1.24 (m, 1H) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz): δ 173.5 (quat, carbonyl), 134.2 (tert, olefine), 130.5 (tert, olefine), 127.9 (tert, olefine), 127.7 (tert, olefine), 46.1 (tert), 45.1 (tert), 39.6 (tert), 34.2 (sec), 23.9 (sec), 20.3 (sec) ppm. CI/MS m/e: 193 (M^++1, 100%), 161 (-H^+, -$NHNH_2$, 17%), 133 (-H^+, -$NHNH_2$, -C=O, 9%), 119 (-H^+, -$NHNH_2$, -C=O, -CH_2, 84%). EI/HRMS m/e: 192.1256 amu (Calc for $C_{11}H_{16}N_2O$: 192.1263 amu).

5-Methylene-tetracyclo[4.4.0.0^{2,8}.0^{4,7}]dec-9-ene (**30**)

A solution of **1** (150 mg, 1.03 mmol) in a small amount of THF was added to freshly prepared

methyltrimethylsilylmagnesium chloride [according to the Bönnemann method[10], using Mg powder (30 mg, 1.2 mmol), a catalytic amount of anthracene, a catalytic amount of MeI (2 drops) and $(CH_3)_3SiCH_2Cl$ (135 mg, 1.10 mmol)] in dry THF (5 ml) at 65°C. After heating under reflux for 16 h. $SOCl_2$ (170 mg, 1.43 mmol) was added. Then, the mixture was cooled in an ice-bath to r.t., hydrolyzed with aqueous saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo*, to give crude **30** as a clear and colorless oil. Purification using flash chromatography (silica gel; pentane) resulted in the isolation of **30** (30 mg, 0.21 mmol, 20%) as clear, colorless oil.

Another way of preparing product **30** was realized by adding BuLi (4 mmol, 2.5 ml of a 1.6 M solution in n-hexane) to a solution of methyltriphenylphosphonium bromide (1440 mg, 4.04 mmol) in Et_2O (20 ml) under an N_2-atm. Then, a solution of **1** (300 mg, 2.05 mmol) in a small amount of Et_2O was added. After 2 h. of stirring the mixture was hydrolyzed with aqueous saturated $NaHCO_3$ and the water phase washed with diethyl ether. The combined ethereal fractions were dried ($MgSO_4$) and concentrated *in vacuo* to give crude **30** (purity 92%). Purification was realized using flash chromatography (silica gel; pentane), to give **30** (190 mg, 1.32 mmol, 64%) as a clear, colorless oil.

IR (CCl_4) ν: 3140-2840 (-C-H unsat.+sat.) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 90MHz) δ: 6.05-5.8 (m, 2H, olefine), 4.4 (s, 2H, $=CH_2$), 3.05-2.05 (m, 6H), 2.0-1.35 (m, 2H, bridge) ppm. ^{13}C-NMR ($CDCl_3$; 15MHz) δ: 153 (quat, $>C=CH_2$), 136.5+132 (tert, olefine(-CH=CH-)), 97 (sec, $>C=CH_2$), 60 (tert), 53.5 (tert), 52 (tert), 49 (tert), 45.5 (tert), 40 (tert), 36 (sec) ppm. EI/MS m/e: 144 (M^+, 27.6%), 129 ($-CH_3$, 100%), 115 ($-CH_3$, $-CH_2$, 26.3%), 105 (10.8%), 91 (29.3%), 77 (19.9%). EI/HRMS m/e: 144.093 amu (Calc for $C_{11}H_{12}$: 144.094 amu).

3-endo-Hydroxy-3-exo-trimethylsilanylmethyl-tetracyclo[5.3.0.0^{2,5}.0^{4,8}]dec-9-ene (**31**)

Trimethylsilanylmethyl chloride (250 mg, 2.05 mmol) was added to a vigorously stirred suspension of freshly crushed Li (35 mg, 5 mmol) in refluxing dried pentane. After 10 h., ketone **1** (290 mg, 1.99 mmol) was added and stirred for another 0.5 h. Then, the reaction mixture was hydrolyzed with aqueous saturated $NaHCO_3$. The water fraction was washed with pentane, the combined organic fractions dried ($MgSO_4$) and concentrated *in vacuo*, to give **31** (418 mg, 1.79 mmol, 90%) as a light yellow oil.

IR (CCl_4) ν: 3580 (-OH), 3100-2800 (-C-H sat.+unsat.) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 90MHz) δ: 6.5 (s, 2H, olefine), 5.1 (t, -OH), 2.95 (m, 1H), 2.7 (m, 5H), 1.45 (s, 2H, bridge), 1.2 (d, 2H, $-CH_2Si(CH_3)_3$), 0.0 (s, 9H, $-CH_2Si(CH_3)_3$) ppm. CI/MS m/e: 235 (M^++1, 5.7%), 234 ($-H^+$, 13.2%), 217 (-OH, 74%), 201 ($-H_2O$, $-CH_4$, 42.7%), 168 (6.1%), 143 ($-Si(CH_3)_3$, $-H_2O$, 54.9%), 129 ($-Si(CH_3)_3$, -OH, $-CH_3$, 23.6%), 108 (37.9%), 91 (15.3%). CI/HRMS m/e: 235.152 amu (Calc for ($C_{14}H_{22}OSi + H^+$): 235.150 amu).

3-Methylene-tetracyclo[5.3.0.0^{2,5}.0^{4,8}]dec-9-ene (**32**)

Alkene **32** was prepared as described for **30**, using BuLi (4 mmol, 2.5 ml of a 1.6 M solution in n-hexane), methyltriphenylphosphonium bromide (1440 mg, 4.04 mmol) in Et_2O (20 ml) and **1** (300 mg, 2.05 mmol) in a small amount of Et_2O. After stirring for 2 days under an N_2-atm., the mixture

was hydrolyzed with aqueous saturated $NaHCO_3$. The water phase was washed with diethyl ether. The combined ethereal fractions were dried ($MgSO_4$) and concentrated *in vacuo* to give crude **32** (purity 85%). Further purification was realized using flash chromatography (silica gel; pentane), to give pure **32** (186 mg, 1.29 mmol, 63%) as a colorless, clear oil.
IR (CCl_4) v: 3100-2850 (-C-H sat.+unsat.) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 90MHz) δ: 6.0 (s, 2H, -CH=CH-), 4.3 (s, 2H, >C=CH_2), 2.95 (m, 2H), 2.7 (m, 4H), 1.6 (s, 2H, bridge) ppm. ^{13}C-NMR ($CDCl_3$; 15MHz) δ: 151 (quat, 1C, >C=CH_2), 133 (tert, 2C, -CH=CH-), 93 (sec, 1C, >C=CH_2), 60 (tert, 1C), 49 (tert, 1C), 48.5 (tert, 2C), 46 (tert, 2C), 31 (sec, 1C, bridge) ppm. EI/MS m/e: 144 (M^+, 2.65%), 143 ($-H^+$, 2.65%), 129 ($-CH_3$, 9.26%), 115 ($-CH_3$, $-CH_2$, 1.53%), 91 (1.22%), 86 (9.91%), 72 (6.8%). EI/HRMS m/e: 144.0935 amu (Calc for $C_{11}H_{12}$: 144.0939 amu).

6-Methylene-tetracyclo[5.4.0.0^{2,9}.0^{5,8}]undec-10-ene (**33**)
Alkene **33** was prepared as described for **30**, using BuLi (4 mmol, 2.5 ml of a 1.6 M solution in n-hexane), methyltriphenylphosphonium bromide (1440 mg, 4.04 mmol) in Et_2O (20 ml) and **7** (320 mg, 2 mmol) in a small amount of Et_2O. After stirring for 2 h under an N_2-atm., the mixture was hydrolyzed with aqueous saturated $NaHCO_3$. The water phase was washed with diethyl ether. The combined ethereal fractions were dried ($MgSO_4$) and concentrated *in vacuo* to give crude **33** (purity 96%). Further purification was realized using flash chromatography (silica gel; pentane), to give pure **33** (278 mg, 1.76 mmol, 88%) as a colorless, clear oil.
IR (CCl_4) v: 3140-2850 (-C-H sat.+unsat.) cm^{-1}. EI/MS m/e: 158 (M^+, 45.6%), 157 ($-H^+$, 24.5%), 143 ($-CH_3$, 87.2%), 129 ($-CH_3$, $-CH_2$, 100%). EI/HRMS (M^+-CH_3) m/e: 143.0861 amu (Calc for $C_{11}H_{11}$: 143.0865 amu).

Tetracyclo[4.4.0.0^{2,8}.0^{4,7}]decan-5-one (**34**)
A catalytic amount of Pd (10% on active carbon) was added to a solution of **5** (600 mg, 4.11 mmol) in methyl acetate (50 ml) and diethylamine (1 ml). Hydrogenation was carried out in a H_2-atm of 40 lbs/inch^2 (± 2.5 atm.) using a Parr-apparatus. After 1 h. a complete transformation into **34** could be observed (GC). The Pd was removed by filtration over hyflo. After concentration *in vacuo* at r.t., **34** (562 mg, 3.80 mmol, 92%) was isolated as a light yellow oil.
IR (CCl_4) v: 2945 + 2870 (-C-H sat.), 1770 (s, -C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 90MHz) δ: 3.15-1.2 (m, 12H) ppm. EI/MS m/e: 148 (M^+, 22.8%), 120 (-C=O, 28%), 105 (25.7%), 91 (55.2%), 79 (100%). EI/HRMS m/e: 148.0896 amu (Calc for $C_{10}H_{12}O$: 148.0888 amu).

Tetracyclo[5.3.0.0^{2,5}.0^{4,8}]decan-3-one (**35**)
Compound **35** was prepared as described for **34**, starting from **1** (600 mg, 4.11 mmol) in methyl acetate (50 ml), diethylamine (1 ml) and a catalytic amount of Pd (10% on active carbon). Hydrogenation was carried out in a H_2-atm of 40 lbs/inch^2 (± 2.5 atm.) using a Parr-apparatus. After 1 h. complete transformation into **35** was observed (GC). The Pd was removed by filtration over hyflo. After concentration *in vacuo* at r.t., **35** (540 mg, 3.65 mmol, 89%) could be isolated as a

partially solidified white product.
IR (CCl_4) v: 2950 + 2870 (s, -C-H sat.), 1795 + 1765 (s, -C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 2.92 (m, 2H), 2.57 (m, 2H), 2.45 (m, 1H), 2.40 (m, 1H), 1.90 (s, 2H, bridge), 1.83 (s, 4H, reduced olefine) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 202.2 (quat, -C=O), 63.2 (tert, 2C), 49.9 (tert, 2C), 48.4 (tert, 1C), 35.5 (sec, 1C, bridge), 33.7 (tert, 1C), 29.2 (sec, 2C, reduced olefine) ppm. EI/MS m/e: 148 (M^+, 42.3%), 120 (-C=O, 48.8%), 105 (32.3%), 91 (87.3%), 79 (100.0%). EI/HRMS m/e: 148.0885 amu (Calc for $C_{10}H_{12}O$: 148.0888 amu).

exo-*4,5-Diazapentacyclo[6.5.0.0^{2,11}.0^{3,7}.0^{9,12}]tridecan-10-one* (**36**)
Ketone **1** (146 mg, 1 mmol) was added to a solution of CH_2N_2(0.3 M, 12 mmol) in Et_2O (40 ml). After stirring for 24 h. at r.t. (reaction was followed with GC), the reaction mixture was concentrated *in vacuo*. Purification with flash chromatography (silica gel, EtOAc/n-hexane=2/1) resulted in pure **36** (114 mg, 61%) as a clear, colorless oil, which solidified at a temperature of -18°C, but turned into an oil at r.t.
IR (CCl_4) v: 2960 + 2870 (s, -C-H sat.), 1765 (s, -C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 5.12 (dm, 1H), 4.55 (dd, 1H), 4.18 (dm, 1H), 3.13 (dm, 1H), 3.05 (td, 1H), 2.95 (td, 1H), 2.55 (m, 2H), 2.30 (m, 1H), 2.02 (bs, 1H), 1.86 (q, 2H, bridge) ppm. CI/MS m/e: 189 (M^++1, 100%), 161 (-C=O/-N_2, 8.41%), 145 (-N_2, -O, 11.30%), 132(-H^+, -C=O, -N_2, 26.45%), 117 (60.99%), 91 (31.86%), 81 (15.35%). EI/HRMS m/e: 188.0954 amu (Calc for $C_{11}H_{12}N_2O$: 188.0950 amu).

exo-*4,5-Diazapentacyclo[6.6.0.0^{2,11}.0^{3,7}.0^{9,12}]quatdecan-3-one* (**37**)
Compound **37** was prepared as described for **36**, using ketone **2** (160 mg, 1 mmol) and CH_2N_2(0.3 M, 12 mmol) in Et_2O (40 ml). After stirring for 24 h. (reaction was followed with GC), the reaction mixture was concentrated *in vacuo*. Purification with flash chromatography (silica gel, EtOAc/n-hexane = 2/1) resulted in pure **37** (150 mg, 0.74 mmol, 74%) as a clear, colorless oil, which solidified at a temperature of -18°C, but turned into an oil at r.t.
IR (CCl_4) v: 2930 + 2860 (s, -C-H sat.), 1770 (s, -C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 4.98 (dm, 1H), 4.48 (ddd, 1H), 3.96 (dt, 1H), 3.05 (dt, 1H), 2.97 (dt, 1H), 2.92 (m, 1H), 2.38 (m, 1H), 2.06 (dt, 1H), 1.83 (m, 1H), 1.74 (m, 4H, bridge), 0.85 (t, 1H) ppm. CI/MS m/e: 203 (M^++1, 100%), 175 (-N_2, 8.2%), 159 (-N_2, -O, 5.0%), 145 (-N_2, -CH_2O, 10.3%), 131 (29.2%), 117 (25.6%), 105 (17.0%), 91 (48.2%), 79 (27.4%). EI/HRMS m/e: 202.1105 amu (Calc for $C_{12}H_{14}N_2O$: 202.1106 amu).

10-endo-*Hydroxy*-exo-*4,5-Diazapentacyclo[6.5.0.0^{2,11}.0^{3,7}.0^{9,12}]tridecane* (**38**)
Compound **38** was prepared as described for **36**, using alcohol **22** (148 mg, 1 mmol) and CH_2N_2(0.3 M, 12 mmol) in Et_2O (40 ml). After stirring for 48 h. (reaction was followed with GC), the reaction mixture was concentrated *in vacuo*. Purification with flash chromatography (silica gel, EtOAc/n-hexane = 2/1) resulted in pure **38** (107 mg, 56%) as a clear, colorless oil.
IR (CCl_4) v: 3350 (s+b, -OH), 2930+2860 (s, -C-H sat.), 1110 (s, -C-O) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 5.91 (dm, 1H), 4.62 (ddd, 1H), 4.20 (dt, 1H), 4.05 (dt, 1H), 3.39 (m, 1H), 3.05 (bs, 1H,

-OH), 2.73 (m, 1H), 2.59 (m, 1H), 2.44 (m, 1H), 2.13 (bs, 1H), 1.96 (m, 1H), 1.86 (bs, 1H), 1.55 (q, 2H, bridge) ppm. CI/MS m/e: 191 (M^++1, 100.0%), 173 (-H_2O, 5.2%), 145 (-H_2O, -C=O/-N_2, 9.9%), 129 (12.6%), 117 (-H_2O, -C=O, -N_2, 8.6%), 105 (16.3%), 95 (14.8%), 79 (19.7%). EI/HRMS m/e: 190.1105 amu (Calc for $C_{11}H_{14}N_2O$: 190.1106 amu).

10-endo-*Acetoxy*-exo-*4,5-Diazapentacyclo[6.5.0.0^{2,11}.0^{3,7}.0^{9,12}]tridecane* (**39**)

Compound **39** was prepared as described for **36**, using acetate **24** (190 mg, 1 mmol) and CH_2N_2(0.3 M, 12 mmol) in Et_2O (40 ml). After stirring for 32 h. (reaction was followed with GC), the reaction mixture was concentrated *in vacuo*. Purification with flash chromatography (silica gel, EtOAc/n-hexane = 2/1) resulted in pure **39** (143 mg, 0.62 mmol, 62%) as a clear, colorless oil.
IR (CCl_4) ν: 2930 + 2860 (s, -C-H sat.), 1730 (s, -C=O), 1225 (s, -C-O) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 5.62 (dm, 1H), 4.88 (dt, 1H), 4.68 (ddd, 1H), 4.10 (dt, 1H), 3.00 (m, 1H), 2.77 (m, 2H), 2.63 (m, 1H), 2.35 (m, 1H), 2.03 (s, 3H, -Me), 2.02 (m, 1H), 1.90 (m, 1H), 1.61 (q, 2H, bridge) ppm. CI/MS m/e: 233 (M^++1, 100.0%), 173 (-H^+, -OC(O)CH_3, 18.1%), 145 (-H^+, -OC(O)CH_3, -N_2, 54.7%), 129 (44.2%), 105 (21.2%), 95 (31.1%), 79 (23.1%). EI/HRMS m/e: 232.1214 amu (Calc for $C_{13}H_{16}N_2O_2$: 232.1212 amu).

10-endo-*Hydroxy*-exo-*4,5-Diazapentacyclo[6.6.0.0^{2,11}.0^{3,7}.0^{9,12}]quatdecane* (**40**)

Compound **40** was prepared as described for **36**, using alcohol **23** (162 mg, 1 mmol) and CH_2N_2(0.3 M, 12 mmol) in Et_2O (40 ml). After stirring for 120 h. (reaction was followed with GC), the reaction mixture was concentrated *in vacuo*. Purification with flash chromatography (silica gel, EtOAc/n-hexane = 2/1) resulted in pure **40** (136 mg, 0.67 mmol, 67%) as a clear, colorless oil.
IR (CCl_4) ν: 3320 (s+b, -O-H), 2930 + 2860 (s, -C-H sat.), 1110 (s, -C-O) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 5.94 (dm, 1H), 4.56 (dd, 1H), 3.94 (t, 1H), 3.84 (dt, 1H), 3.34 (m, 1H), 2.69 (m, 2H, also -OH), 2.51 (m, 1H), 2.38 (m, 1H), 1.88 (dt, 1H), 1.65 (m, 4H, bridge), 1.32 (bs, 1H), 0.75 (bs, 1H) ppm. CI/MS m/e: 205 (M^++1, 100%), 187 (-H_2O, 12.8%), 159 (-H_2O, -N_2, 5.5%), 145 (-H_2O, -N_2, -CH_2, 6.5%), 131 (8.5%), 119 (59.5%), 107 (12.6%), 91 (59.8%), 79 (24.0%). EI/HRMS m/e: 204.1266 amu (Calc for $C_{12}H_{16}N_2O$: 204.1263 amu).

10-endo-*Acetoxy*-exo-*4,5-Diazapentacyclo[6.6.0.0^{2,11}.0^{3,7}.0^{9,12}]quatdecane* (**41**)

Compound **41** was prepared as described for **36**, using acetate **25** (204 mg, 1 mmol) and CH_2N_2(0.3 M, 12 mmol) in Et_2O (40 ml). After stirring for 48 h. (reaction was followed with GC), the reaction mixture was concentrated *in vacuo*. Purification with flash chromatography (silica gel, EtOAc/n-hexane = 2/1) resulted in pure **41** (155 mg, 0.63 mmol, 63%) as a clear, colorless oil.
IR (CCl_4) ν: 2930 + 2860 (s, -C-H sat.), 1730 (s, -C=O), 1225 (s, -C-O) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 5.52 (dm, 1H), 4.55 (m, 2H), 3.85 (dt, 1H), 2.86 (m, 1H), 2.64 (m, 2H), 2.54 (m, 1H), 1.97 (s, 3H, -Me), 1.86 (d, 1H), 1.65 (m, 4H, bridge), 1.52 (bs, 1H), 0.72 (bs, 1H) ppm. CI/MS m/e: 247 (M^++1, 74.6%), 233 (-CH_2, 7.2%), 205 (-C=O, -N_2, 20.6%), 187 (-H^+, -OC(O)CH_3, 29.8%), 159 (-H^+, -OC(O)CH_3, -N_2, 27.4%), 143 (24.6%), 131 (40.0%), 117 (49.6%), 105 (31.2%), 91 (88.3%),

79 (43.1%). EI/HRMS m/e: 246.1371 amu (Calc for $C_{14}H_{18}N_2O_2$: 246.1368 amu).

5-Oxapentacyclo[6.4.0^{2,6}.0^{3,10}.0^{7,9}]dodecan-4-one (**42**)

A solution of bromine (100 mg, 0.63 mmol) in CCl_4 (10 ml) was added to a solution of ketone **2** (100 mg, 0.63 mmol) in CCl_4 (10 ml). After stirring for 10 min. the organic mixture was washed with 2% aqueous $Na_2S_2O_5$ (5 ml) and the resulting water fraction extracted with CCl_4 (10 ml). The combined organic fractions were washed with water (2 × 2 ml and 1 × 5ml), dried ($MgSO_4$) and concentrated *in vacuo*, to give crude **42** (purity 72% (GC)). Purification using flash chromatography (silica gel, n-hexane/EtOAc=3/1) resulted in **42** (80 mg, 0.45 mmol, 73%) as a white solid (purity 97%).

A pure sample of **42** was obtained by sublimation (80°C, 3 mm Hg).

IR (KI) ν: 3050 (w, cyclopropane C-H), 3000-2860 (-CH sat.), 1760 (-C=O, lactone; in CCl_4 1780) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 5.12 (dd, 1H), 2.63 (q, 1H), 2.37 (m, 1H), 2.25 (m, 1H), 2.19 (bd, 1H), 1.73-1.57 (m, 5H), 1.49 (m, 1H), 1.17 (q, 1H) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 180 (quat, -C=O), 84 (tert, -C-O), 44 (tert), 43 (tert), 30 (tert), 25 (sec, bridge), 24 (tert), 22 (tert, probably cyclopropane), 21 (tert, probably cyclopropane), 19 (sec, bridge), 16 (tert, probably cyclopropane) ppm. CI/MS m/e: 177 (M^++1, 99%), 159 (-OH, 23%), 148 (-CO, 6%), 132 (-CO_2, 100%), 117 (54%), 104 (28%), 91 (72%), 78 (23%). EI/HRMS m/e: 176.0837 amu (Calc for $C_{11}H_{12}O_2$: 176.0837 amu).

3.5 References and notes

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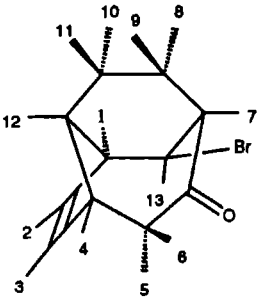
3.6 Structure elucidation of 11-bromotricyclo[5.3.1.$0^{4,8}$]undec-5-en-2-one 10 by ^{1}H-NMR analysis.

The exact position of all protons in the ^{1}HNMR spectrum of **10** was established using 2D ^{1}H-NMR Cosy and NOE-difference techniques. Proton 13, which is the proton geminal to the bromine substituent and which has a resonance at δ 4.07 has been used as starting point in this analysis. The data collected in these experiments are collected in table 3.4.

Table 3.4 Results of NMR-experiments with compound **10**



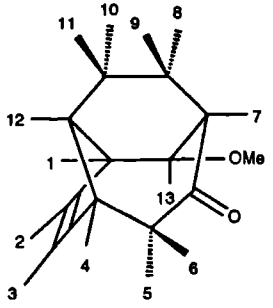
No	2	3	13	1	6	4	7	12	8	5	11	10	9
δ	5.83	5.73	4.07	3.23	3.05	2.76	2.73	2.65	2.36	2.27	2.23	2.05	1.93
2		X	N	X,N									
3	X			X		X,N				N			
13	N						X						X
1	X,N	X						X					
6						X				G			
4		X,N			X			X					
7			X						X				
12				X		X					X	X	
8							X				X		G
5					G								
11								X	X			G	X
10								X			G		X
9			X						G		X	X	

X=coupling G=geminal coupling N=NOE-contact

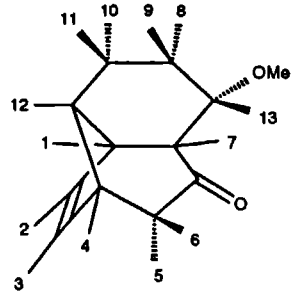
3.7 Structure elucidation of 11-methoxytricyclo[5.3.1.$0^{4,8}$]undec-5-en-2-one 11 by ^{1}H-NMR analysis.

Since it appeared impossible to unambiguously assign the proton geminal to the methoxy group in the ^{1}H-NMR spectrum, this proton could not be taken as a starting point for the ^{1}HNMR-analysis of 11. Instead the methoxy group together with the olefinic protons have been taken as reference. The data obtained are collected in table 3.5. All these data are in accordance with

Table 3.5 The results of the Cosy- and NOE-data of the rearranged product with an incorporated methoxy group



11



11a

No	2	3	MeO	1	6	4	7	12	13	5				
δ	5.78	5.71	3.30	3.07	3.04	2.77	2.77	2.66	2.60	2.26				1.76
2		X		N				X,N	n					
3	X					X,N		N		N				
MeO				N			N	n						
1	N		N			X								
6						X				G				
4		X,N		X	X									
7			N						X				X	
12	X,N	N	n						X					
13	n						X	X						
5		N			G									
												G	X	X
											G		X	X
							X				X	X		G
											X	X	G	

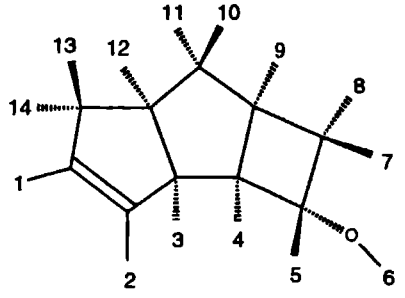
X=coupling G=geminal coupling N=NOE-contact n=weak NOE-contact

structure 11 and not with 11a therefore eliminating structure 11a as the alternative structure.

3.8 Structure elucidation of tricyclo[5.3.0.0^{2,5}]dec-9-en-exo-3-ol 28 by ^{1}H-NMR analysis.

The data obtained from the 2D ^{1}H-NMR Cosy spectrum and the NOE-difference spectrum of 28 are collected in table 3.6. Starting point in this analysis is the olefinic signal at δ 5.65. The data

Table 3.6 Data obtained from the 2D ^{1}H-NMR Cosy spectrum and the NOE-difference spectrum for the olefinic protons of compound 28



28

No	1+2	5	3	12	4+6	9+14	10	13	7	8	11
δ	5.65	4.19	3.22	2.76	2.64	2.44	2.16	2.10	2.00	1.90	1.02
1+2		N	x,N			x,N		x,N			
5	N				X				X	X	
3	x,N			X	X						
12			X			X	X				X
4+6		X	X			X					
9+14	x,N			X	X			G1		X	X
10				X							G2
13	x,N					G1					
7		X								G3	
8		X				X			G3		
11				X		X	G2				

olefin — 1H is of the OH group

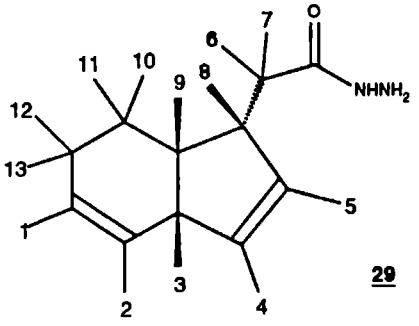
X=coupling x=small coupling N=NOE contact G=geminal coupling

obtained are in full accord with the proposed structure 28.

3.9 Structure elucidation of 6-(bicyclo[4.3.0]nona-2,7-dienyl)-acetic acid hydrazide 29 by ^{1}H-NMR analysis.

The data obtained from the 2D ^{1}H-NMR Cosy spectrum of **29** are collected in table 3.7.

Table 3.7 Results of the 2D ^{1}H-NMR Cosy spectrum for compound **29**



29

No	1+2	5	4	8	3	9	6 or 7	6 or 7	12+13	10 or 11	10 or 11
δ	5.8	5.65	5.5	3.35	3.2	2.5	2.3	2.2	1.94	1.4	1.2
1+2					x				x		
5			X	x							
4		X			x						
8		x			x	X	X	X			
3	x		x	x		X					
9				X	X					x	X
6 or 7				X				G			
6 or 7				X			G				
12+13	x									X	X
10 or 11						x			X		G
10 or 11						X			X	G	

olefin

X=coupling x=small coupling G=geminal coupling

Starting point for this analysis is the olefinic signal at 5.8 ppm. This ^{1}H-NMR analysis fully confirms structure **29**.

CHAPTER 4

INTRAMOLECULAR REACTIONS OF STRAINED HALF-CAGE SYSTEMS CONTAINING AN ALCOHOL AND AN OLEFIN FUNCTION IN CLOSE PROXIMITY.

4.1 Introduction.

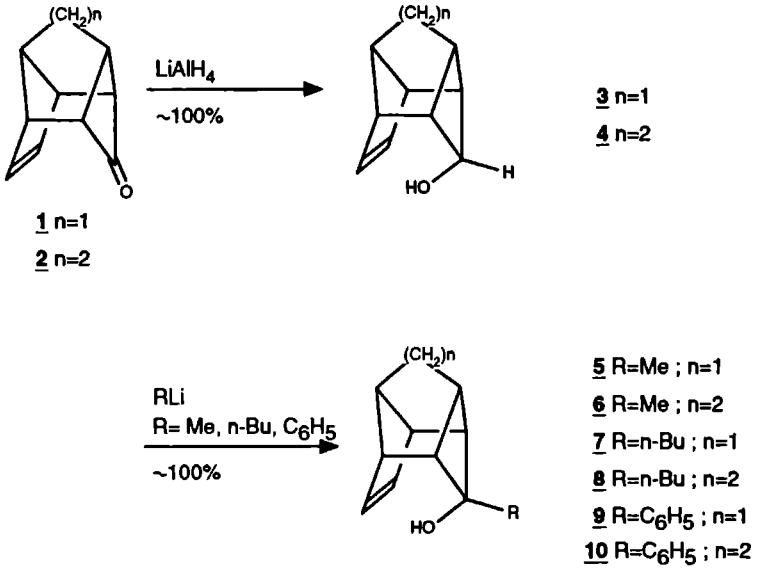
In the preceding chapter the reduction of 2,9-carbonyl-brend-4-ene **1** and its homologue 2,9-carbonyl-1,8-homo-brend-4-ene **2** with lithium aluminum hydride to give *endo*-alcohols **3** and **4**, respectively, was reported. In a similar way reaction of tetracyclic ketones **1** and **2** with alkyl lithium compounds leads to the related *endo*-alcohols **5** and **6** (R=Me), **7** and **8** (R=n-Bu), **9** and **10** ($R=C_6H_5$), respectively (Scheme 4.1). The alcohol function in all these cage-type alkenols is positioned in close proximity to the olefinic bond. Both the NMR- and IR-spectral data clearly show that there is a considerable non-bonding interaction between the hydroxylic and olefinic function in these strained cage alcohols (section 3.2.2.2 + 3.2.2.3). The occurrence of an alkene and alcohol function enforced in close proximity make these alcohols **3**-**10** ideal substrates to study the intramolecular alcohol addition to an non-activated isolated olefinic bond[1]. Reactions of water and alcohols with non-activated double bonds catalyzed by enzymes are known phenomena in nature, but not yet completely understood. The origin of these processes probably lies in the presence of a hydroxyl group in the near vicinity of the olefinic bound. Apparently, appropriate enzymes are able to enforce the required transition state by positioning the olefinic substrate and the nucleophile, *e.g.* a water molecule, on the active site at just the required intermolecular distance. Simulation of such a transition state can be envisaged in strained polycyclic alcohols, such as **3**-**10**, which exhibit strong steric compression. This chapter reports on the intramolecular nucleophilic addition of the *endo*-hydroxyl group to the alkene moiety in the strained alkenols **3**-**10**.

At the time when this study began the intramolecular nucleophilic addition of an alcohol group to a non-activated olefin function in a rigid polycyclic system had been reported by two groups[2-11]. A summary of these studies involving compounds **11**-**18** is given in Scheme 4.2.

One of the first examples of a nucleophilic addition of an alcohol function to a non-activated double bond under basic conditions was reported by Grob and Katayama[2]. Treatment of **11** with sodium ethoxide in ethanol gave oxaadamantane **19** in 50% yield. The close proximity of the hydroxyl function and the olefinic moiety in **11** was demonstrated by the observation of a strong non-bonding interaction *viz.* hydrogen bonding, as evidenced by the spectral features of **11**.

The *endo*-polycyclic alkenols (for convenience named as polycyclenols) **12**-**17** were extensively studied by Ganter et al[3-5]. These authors showed that these compounds generally undergo effective ring closure to polycyclic ethers **20**-**25** under basic conditions. In all the polycyclenols **12**-**17** a strong non-bonded intramolecular interaction between the alkohol and olefin

Scheme 4.1

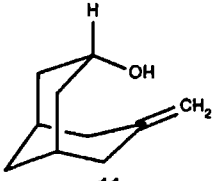


function was observed. The presence of an alkyl group at the carbinyl carbon led to considerable enhancement of the reaction rate for alcohol addition as the result of increased compression. An X-ray analysis of the n-Bu analogue of **13** (R=n-Bu) gave clear evidence for hydrogen bonding between the hydroxyl function and the olefinic moiety[6].

Polycyclenols **18** undergo a quantitative conversion into **26** on treatment with potassium t-butoxide in t-butyl alcohol at 80 °C[7]. Again the effect of an alkyl group at carbinyl carbon on the rate of intramolecular addition is striking.

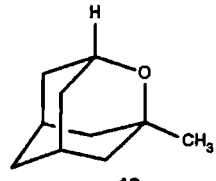
The polycyclenols **3** and **4** are structurally closely related to Ganter's structures **12**-**18**. In particular the similarity between oxa-bridge structure **12** and **3** is evident. These structures differ only in the size of the ring to which the alcohol function is attached, *viz.* a five-membered ring in **12** and a four-membered ring in **3**. An essential difference between all the structures mentioned in Scheme 4.2 and tetracyclenols **3** and **4** is that the latter compounds are considerably more strained. The strain energy of the most strained alcohol in Scheme 4.2, *viz* **12**, amounts to 48 kcal/mole whereas the strain energies of **3** and **4** are 65 and 72 kcal/mole, respectively.

Scheme 4.2

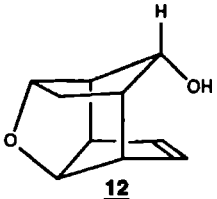


11

NaOEt/EtOH; 50%

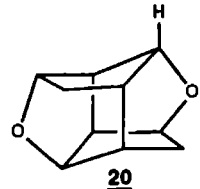


19

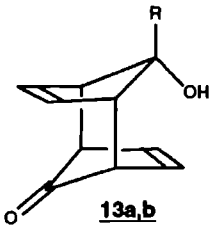


12

2N aq. NaOH/CH_3OH 1:1; 67°C; 40h.; 87%



20



13a,b

a R=H

1 mol tBuOK/tBuOH; 25°C; 0.4h.; quant

2N aq. NaOH/CH_3OH 1:1; 25°C; 90h.; quant.

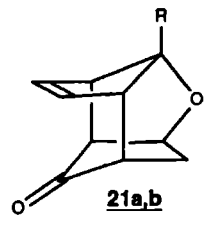
2N aq. NaOH/CH_3OH 1:1; 50°C; 8h.; quant.

b $R=CH_3$

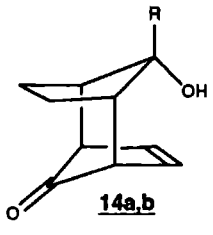
2N aq. NaOH/CH_3OH 1:1; 0°C; 2h.; quant.

2N aq. NaOH/CH_3OH 1:1; 25°C; 0.12h.; quant.

0.2 N aq. NaOH/CH_3OH 1:1; 25°C; 1.2h.; quant.



21a,b



14a,b

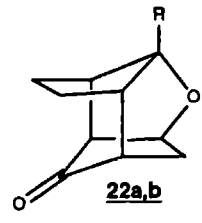
a R=H

2N aq. NaOH/CH_3OH 1:1; 25°C; 340h.; 60%

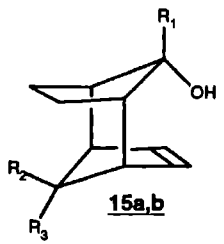
2N aq. NaOH/CH_3OH 1:1; 50°C; 50h.; quant.

b $R=CH_3$

2N aq. NaOH/CH_3OH 1:1; 25°C; 2.5h.; quant.



22a,b



15a,b

a $R_1=R_2=R_3=H$

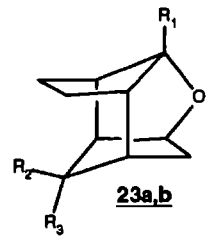
1 mol tBuOK/tBuOH; 82°C; 24h.; 50%

b $R_1=CH_3;R_2=R_3=H$

1 mol tBuOK/tBuOH; 25°C; 24h.; quant.

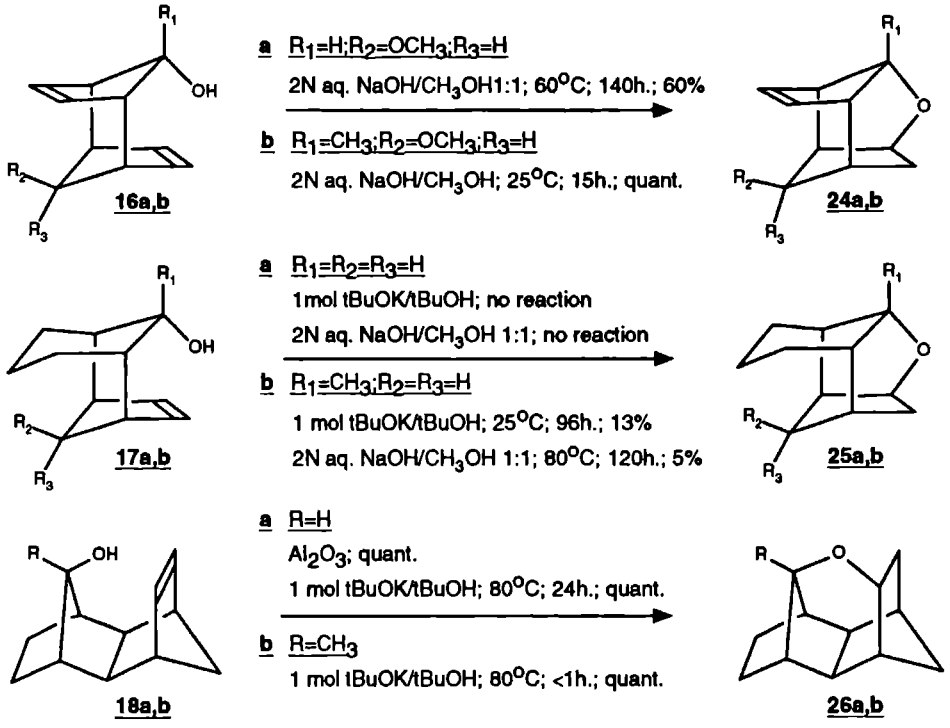
2N aq. NaOH/CH_3OH 1:1; 25°C; 340h.; 70%

2N aq. NaOH/CH_3OH 1:1; 50°C; 190h.; quant.



23a,b

Scheme 4.2

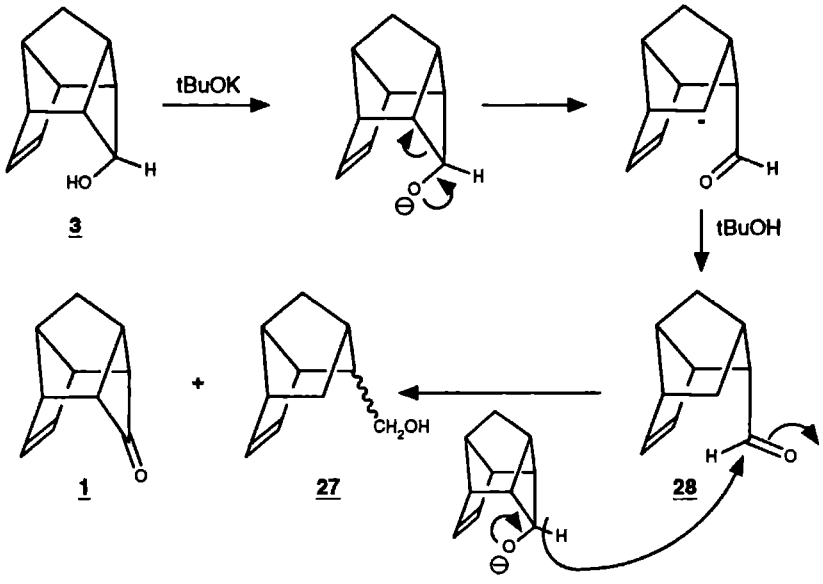


4.2 Base-induced intramolecular addition reaction in 10-*endo*-2,9-methano-brend-4-ene-10-ol 3 and 11-*endo*-2,9-methano-1,8-homo-brend-4-ene-11-ol 4.

The ring closure of polycyclenol 3 was attempted first. Treatment of 3 using the conditions as applied by Ganter[5] for the closure of 12 (Scheme 4.2), *viz.* 2 N aqueous sodium hydroxide in methanol (1:1), did not give, the desired ring closure even not after prolonged reaction times. No product could be isolated or identified. Most of the starting material was recovered unchanged. However, when potassium *t*-butoxide in *t*-butyl alcohol was used as the base a reaction was observed leading to the unexpected formation of carbonyl brendene **1** and polycyclenol 27 in a ratio of 1:1 (Scheme 4.3). No products derived from initial intramolecular alcohol addition to the olefinic bond were detected.

The formation of both products can be rationalized by invoking a hydride transfer from polycyclenol 3 to the tricyclic aldehyde 28 which is assumed to be the initial product formed in a base induced opening of the starting alcohol (Scheme 4.3). Both this cyclobutanol ring opening and

Scheme 4.3

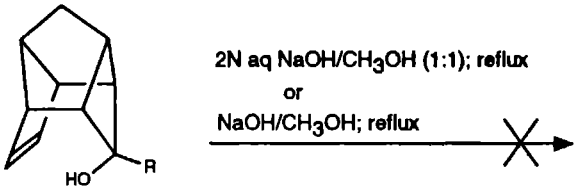


the subsequent reduction of the aldehyde function has some precedent in the literature. The initial cyclobutanol ring opening is an example of a nucleophilic eliminative ring fission in which a C=O double bond is formed by elimination of a C-leaving group. Such an elimination requires either relief of ring strain or substantial stabilization of the leaving-group, or both[12]. Evidently, for **3** the release of ring strain is the determining factor in directing the product formation. This cyclobutanol ring cleavage which in essence is a homoketonization reaction[13], is apparently more favorable than the intramolecular addition of the *endo*-alcoholate function to the double bond. Since no aldehyde **28** was isolated, but only the corresponding alcohol, fast reduction of **28** must have taken place. The formation of ketone **1** in about the same yield as alcohol **27** already indicates a reduction/oxidation process involving alcohol **3** as the hydride donor. Such a process of intermolecular hydride transfer involving an alcohol and a carbonyl compound has precedents in the reversible Meerwein-Ponndorf-Verley reduction/Oppenauer oxidation process[14]. Both the occurrence of a facile homoketonization of **3** and the subsequent rapid hydride transfer from **3** to aldehyde **28** points to the labile character of the alcoholate of **3** which may be the result of strong electrostatic repulsion between the olefinic π-systems and the alcoholate anion.

It was also tried to accomplish an intramolecular alcohol addition for the *endo* alcohols **5**, **7** and **9** having an extra substituent at the carbinol carbon atom, using either aqueous sodium hydroxide in methanol (1:1) or an anhydrous solution of sodium hydroxide in methanol as the base, however again without success (Scheme 4.4).

The homologous polycyclenol **4** behaved entirely different upon treatment with base.

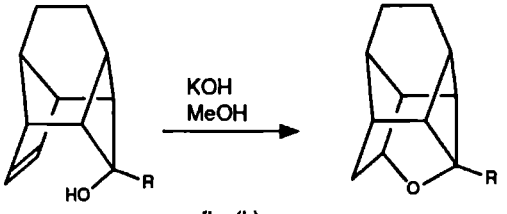
Scheme 4.4



3 R=H **7** R=n-Bu
5 R=CH_3 **9** R=C_6H_5

Treatment of **4** with 2 N aqueous sodium hydroxide in methanol (1:1) gave, after heating at reflux for 40 h, ring closure to **29** in 62% yield. When the heating was continued for a longer period decomposition of **29** took place. The formation of decomposition products severely complicated the isolation of the cyclization product **29**. By using anhydrous potassium hydroxide in methanol oxacage **29** was obtained in an excellent yield of 70% by heating at reflux for 24 h without difficulties (Scheme 4.5). The absence of water appeared to be crucial in avoiding subsequent decomposition of **29**.

Scheme 4.5



	reflux(h)		yield
4 R=H	24	**29** R=H	70%
6 R=CH_3	1	**30** R=CH_3	94%
8 R=n-Bu	1	**31** R=n-Bu	92%
10 R=C_6H_5	0.33	**32** R=C_6H_5	93%

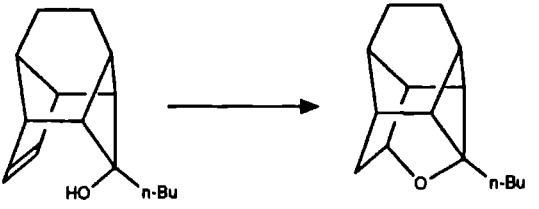
The structure of oxacage **29** was readily deduced from its spectral data. The IR-spectrum lacked an OH absorption, while an exact mass measurement revealed the gross composition $C_{11}H_{14}O$. Careful analysis of the ^1H- and ^{13}C-NMR spectra unambiguously confirmed the presence of an ether bridge and allowed assignment of most of the observed resonances. Both the carbinol and olefinic signals, typical for **4**, were entirely absent in the spectra of **29**.

The homo-brendenols **6**, **8** and **10**, which have the same basic structure as **4** but possess an extra alkyl or aryl group at the carbinyl position, were subjected to the same basic conditions

(Scheme 4.5). In all cases the respective oxacage compounds **30**, **31** and **32** were produced in excellent yields. As expected on the basis of Ganter's results[15], it was found that these tertiary carbinols react much faster than parent homo-brendenol **4** (Scheme 4.5). The structures of the respective compounds **30**, **31** and **32** were secured by their spectral data (see Experimental Part).

In order to gain insight in the scope of this intramolecular ether formation, the cage closure reaction of polycyclenol **8** containing a butyl substituent, was studied with a variety of bases (Scheme 4.6). It was found that the best result were obtained with either sodium or potassium hydroxide in an alcoholic solvent. No ether formation was observed at all when bases were used in aprotic solvents. When **8** was heated at reflux in either protic or aprotic solvents, in the absence of base no reaction was observed at all.

Scheme 4.6



8 **31**

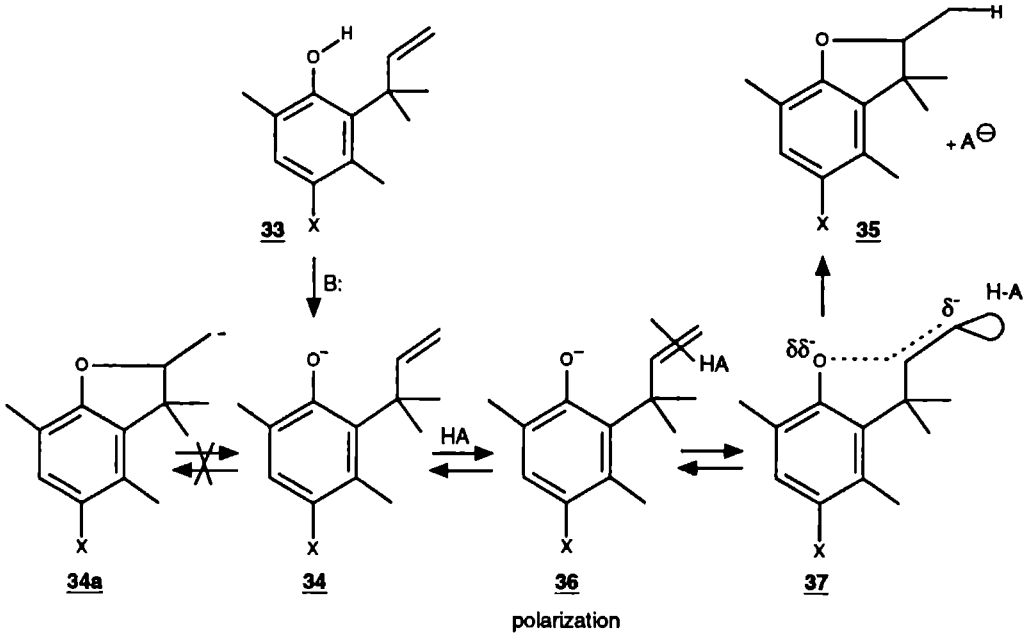
conditions	time	% of cage closure
MeOH/KOH reflux	1h	92
4N NaOH/MeOH (1:1) reflux	3h	90
THF/NaOMe reflux	24h	-
Hexane, reflux (no base)	24h	-
Hexane, Et_3N, reflux	2h	-
MeOH, reflux (no base)	24h	-

4.3 Discussion of the mechanism of the cage closure reaction.

The first detailed description of a mechanism concerning an intramolecular nucleophilic addition reaction of a hydroxy group to a non-activated double bond was given by Evans and Kirby[1]. The reaction at issue involved the intramolecular addition of a phenolate oxygen to the neighboring

ethylene moiety in phenols **33** (Scheme 5.6). In these phenols the conformation is locked in such a way that the olefinic double bond is in close proximity to the phenolic group and therefore these substrates were considered suitable models for olefin hydration. Indeed these phenolic olefins **33** readily undergo intramolecular cyclization to the corresponding ethers **35** when treated with a variety of bases in aqueous acetonitrile. It appears that this addition is nucleophilic in nature. Kinetic evidence revealed that the most likely mechanism involves pre-association of the phenolate anion **34** and some general acid, *e.g.* a protic solvent. Addition of the phenoxide anion to the alkene will in principle give the primary carbanion **34a** but this is expected to be a prohibitive high-energy species. The full development of such a high-energetic species is however not required if a proton source is already present in an appropriate position as the primary carbanion centre develops. Such a situation can be best envisaged by complex **37**. Proton transfer begins then at a point where a substantial amount of negative charge has developed on the terminal methylene group and leads to almost immediate stabilization of the system. Thus, the transition state is reached when proton transfer begins. The bond to the general acid is therefore very weak in the transition state, accounting for the almost complete insensitivity to its pK_a, and the low solvent deuterium isotope effect observed for this reaction. A mechanistic representation of the overall process based on these considerations is given in Scheme 4.7.

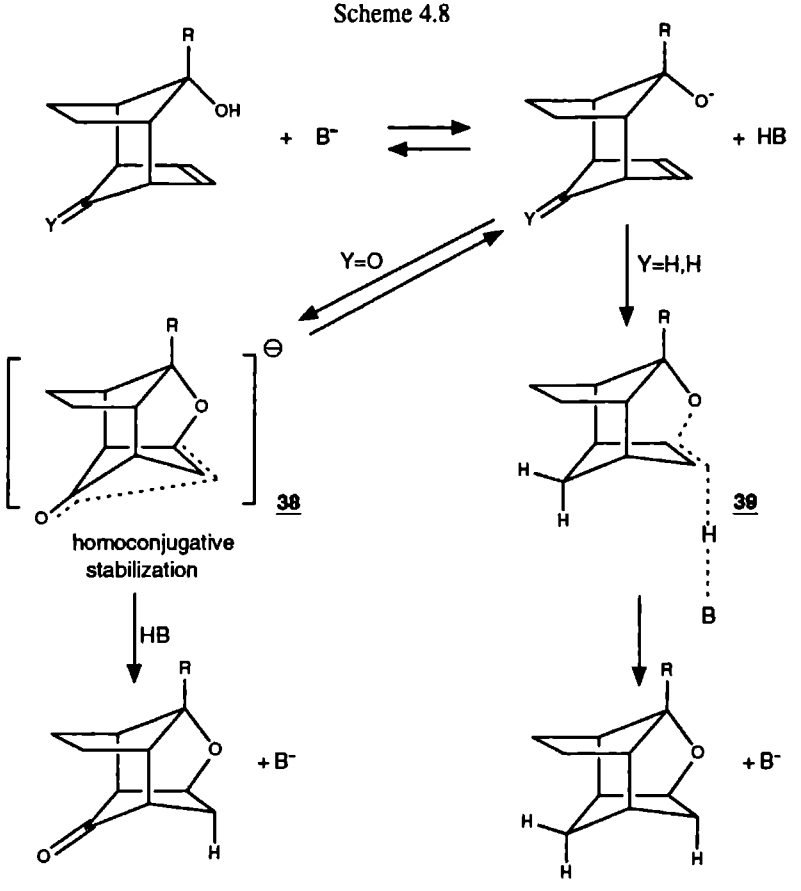
Scheme 4.7 Mechanism of addition to isolated olefinic bond[1]



A similar mechanistic explanation for the results of the base catalyzed intramolecular nucleophilic addition of an alkoxide anion to an olefinic bond in polycyclenols **12**-**17**, is given by

Ganter *et al.*[15] In these cyclenols the carbon double bond is not activated by electron-attracting substituents. Their mechanistic model is based on kinetic data collected for the reactions of **12**-**17** with a variety of hydroxylic bases in methanol. The mechanism proposed is depicted in scheme 4.8.

Scheme 4.8



All conversions investigated are pseudo-first order reactions independent of the nature of the cation of the hydroxylic base used. Isotope studies point to a transition state with strong carbanionic character. In the first step a reversible deprotonation of the alcohol moiety takes place. For the subsequent reaction there are two well distinguished pathways, *viz.* (a) one for substrates with an additional carbonyl group which cyclizes via a homoenolate-like intermediate **38** followed by stereoselective protonation from the *exo*-side by the hydroxylic solvent, and (b) one for substrates without a carbonyl group which undergo ring closure through carbanion-like transition state **39** followed by proton transfer from the hydroxylic solvent already disposed at the *exo*-side in the transition state. By using D-labeling these stereoselective *exo*-protonations could be proven, showing that the above proton transfers from the solvent are directly coupled with the ether bond formation.

Homoconjugative stabilization as proposed for ketones **13** and **14** leads typically to rate enhancements between 10^2-10^4 as compared with the polyenols **15**-**17** which lack a carbonyl function. Another important factor that strongly affect the rate of addition of the alkoxide anion to the olefinic bond in substrates **12**-**17** is steric compression. Steric compression between the alcoholate group and the carbon double bond may be achieved in two principal ways: *viz.* by changing the substitution pattern at carbinyl carbon atom *e.g.* by introducing alkyl or aryl groups, or by modification of the polycyclic skeleton *e.g.* by changing ring sizes. The effect of ring size is most dramatically demonstrated for **15a** and **17a**. Going from a five-membered ring in **15a** to a six-membered ring in **17a** releases the steric compression in such a way that hardly any cyclization is observed for **17a**, whereas under identical conditions cyclic ether **23a** is formed in 50% yield. The effect of carbinyl substitution is also clearly illustrated by the data in Scheme 4.2. Substitution of the carbinyl hydrogen atom by an alkyl or aryl group causes a strong pyramidalization of the carbinyl carbon atom, which leads to an increase of steric compression between the hydroxyl function and the olefinic bond. Typical cyclization rate enhancements observed for methyl substituted polycyclic enols as compared with the unsubstituted compounds are 50-100 fold.

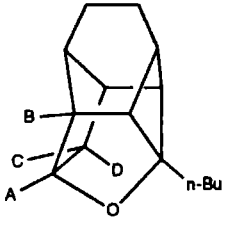
The mechanistic model for base induced intramolecular nucleophilic addition to a non-activated carbon double bond as proposed by the groups of Kirby[1] and Ganter[15] can be used to explain our experimental findings for the reactions of tetracycloenols **3**-**10** upon treatment with base. The inability of brendenols **3**, **5**, **7** and **9** to undergo cyclization to the corresponding oxacage compounds shows that for these tetracyclenols apparently no acceptable transition state can be reached to allow intramolecular alcoholate addition to the carbon double bond. Extending the C_1-C_4 methylene bridge in these brendenols to an ethylene bridge changes the structural features of the tetracyclic ring system in such a way that alcoholate addition becomes an effective process. Molecular modeling using AM1 calculations show that the interatomic distances between the oxygen anion and the nearest olefinic carbon in the alcoholates of **3** and **4** are 2.63 and 2.55[5] Å, respectively. For the alcoholate of Ganter's polycyclenol **12** which rapidly undergoes intramolecular addition, this interatomic distance is 2.55 Å. Thus, the oxygen anion in the alcoholate of **4** has moved toward the olefinic double bond as the result of the outbending effect of the ethylene bridge as compared with the methylene bridge. As a consequence the steric compression between the olefinic bond and the alcoholate function has increased considerably. This is reflected in the increased strain energy of alcohol **4** (SE 72 kcal/molc) as compared with **3** (SE 65 kcal/mole) and also in the relatively fast and oxacage formation observed for **4**. A more detailed analysis of the effect of structural features on the transition state of these base-catalyzed intramolecular alcoholate additions using Minimum Energy Reaction Path calculations is given in section 4.4.

Analogous to the work of Ganter, a considerable influence of substitution at the carbinyl carbon in homobrendenol **4** on the effectiveness of the intramolecular nucleophilic addition is observed (Scheme 4.2). Replacing the H-atom in **4** by a methyl, butyl or phenyl group results in an increased pyrimidalization of the carbinyl carbon which leads to more steric compression. This phenomenon is nicely reflected in the respective reaction rates and chemical yields observed for the

oxacage formation from the homobrendenols **4**, **6**, **8** and **10** (Scheme 4.5). This accelerating effect of pyrimidalization at the carbinyl carbon on the base-catalyzed intramolecular addition is apparently not sufficient to enforce an oxacage closure of the brendenols **5**, **7** and **9**.

Assuming that the mechanism as depicted Scheme 4.8 is also valid for the base-induced intramolecular cyclization in the homobrendenol system, protonation of the transient carbanionic species should be a stereoselective process which, due to electronic and steric implications should occur preferentially from the *exo*-face of the molecule. In order to establish the stereochemistry of this process a D-labeling experiment seems appropriate. For this purpose the ^{1}HNMR-spectrum of the n-butyl substituted pentacyclic ether **31** was analyzed using 2D-NMR techniques. In particular the signals of protons C en D in **31** had to be established unambiguously (figure 4.1). Starting point in this analysis is proton A which is readily recognized at δ 4.65 ppm. NOE and decoupling experiments revealed the positions and the multiplicity of protons B, C and D. Proton A was found to have three H-couplings, two of 4.8 Hz and one of 1.7 Hz. Molecular modeling of compound **31** showed that the torsion-angles of proton A with protons B and C are very small in contrast to that with proton D which is almost 90°. From this structural information it can be concluded that the coupling between proton A and protons B and C amounts to 4.8 Hz, wheras the coupling between A and D is 1.7 Hz. The NOE-difference spectrum led to three proton signals: one at δ 2.66 ppm and

Figure 4.1



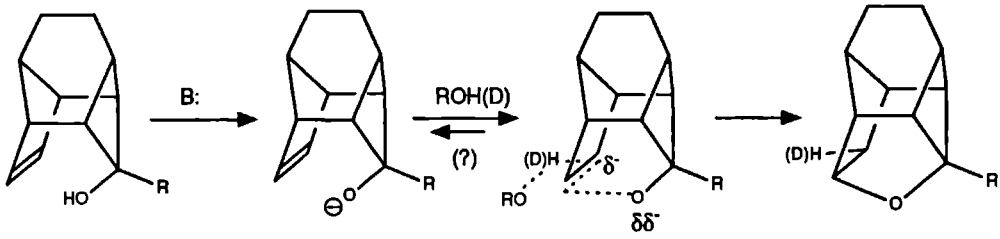
31

two partially overlapping signals at δ 1.44 and 1.41 ppm. Decoupling experiments showed that these three signals are coupled with the signal of proton A. Irradiating at δ 2.66 ppm caused the disappearance of one 4.8 Hz coupling. The magnitude of the coupling for the signals around 1.4 ppm could not be estimated because of the overlap between these two signals.

Deuterium incorporation was accomplished by performing the intramolecular cyclization of **8** with potassium methoxide in deuteromethanol (CH_3OD). The ^{1}NMR-spectrum of deuterated **31** showed the incorporation of one deuterium atom resulting in the disappearance of the signal at δ 1.41 ppm. The signal at 2.66 ppm was not affected by the deuteration proving that proton B is responsible for this resonance. As expected deuteration did affect the multiplicity of proton A. The relatively large coupling of 4.8 Hz had completely disappeared whereas the H-coupling of 1.7 Hz was not affected. This observation leads to the conclusion that proton C is replaced by deuterium in monodeuterated **31** proving that deuteration (and protonation) of the intermediate carbanionic

intermediate **40** takes place exclusively from the *exo*-face of the molecule (Scheme 4.9). Hence, it may be concluded that the base-induced intramolecular alcoholate additions observed for the homobrendenol system **4** follows a mechanistic pathway similar to that proposed by Kirby[1] and Ganter[15] for their alkenols (Scheme 4.9). The determining factor for these additions to occur is release of steric energy due to considerable steric compression between the alcoholate anion and the olefinic bond.

Scheme 4.9



4 R=H
6 R=CH_3
8 R=nBu
10 R=C_6H_5

40

41

29 R=H
30 R=CH_3
31 R=nBu
32 R=C_6H_5

4.4 Minimum energy reaction path calculations

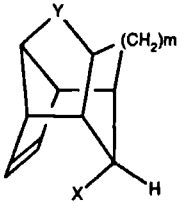
The remarkable difference in behavior of the brendenol system **3** and homobrendenol system **4** in the base-induced oxacage closure reactions was a reason to study the effect of a skeletal change on the minimum energy reaction path leading to intramolecular cyclization, in somewhat more detail. A rather qualitative explanation for the inreactivity of **3** is already given in the section above. In this section the results of Minimum Energy Reaction Path (MERP) calculations for the base-catalyzed ether formation from **3**, **4** and **12** will be presented. The latter compound is added because its structure resembles that of **3** and **4**.

A MERP-calculation is the simplest procedure to find the transition state (TS) for a reaction R → P. For this purpose the change in energy is calculated as a function of a suitable reaction coordinate. At each point the energy is minimized with respect to all other coordinates at each point. This will eventually result in a potential surface joining R to P. The highest point in this path corresponds to the transition state (TS).

Before actually starting the MERP-calculations it is required to decide about the reaction coordinate that is suitable for the reaction under study. Based on the accepted mechanism for the base-catalyzed intramolecular nucleophilic addition to non-activated alkenes (see section 4.3) it is evident that the rate determining step will be attack of the alcoholate anion on the olefinic function.

Therefore, the transition state relevant for this MERP-calculation is positioned on the reaction coordinate somewhere between the stage of the deprotonated alcohol **40** and the formation of the carbanion **41**. Thus, the pertinent reaction coordinate will be the distance line between the oxygen anion and the reacting olefinic carbon atom. Starting point on this reaction coordinate is the alcoholate anion. Energy minimization of the alcoholates derived from **3**, **4** and **12** was accomplished using AM1. The energies calculated for these alcoholates **42**, **43** and **44**, and their respective alcohols are listed in Table 4.1. The distance between the oxygen anion and the nearest olefinic carbon atom in **42**, **43** and **44** is also given. side.At the product side carbanions **45**, **46** and **47** are considered as the

Table 4.1



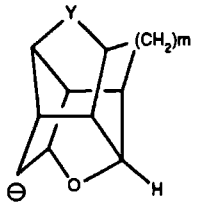
3 Y=CH_2, m=0, X=OH
4 Y=CH_2-CH_2, m=0, X=OH
12 Y=O, m=1, X=OH
42 Y=CH_2, m=0, X=O^-
43 Y=CH_2-CH_2, m=0, X=O^-
44 Y=O, m=1, X=O^-

structure	heat of formation (kcal/mole)	deprotonated structure	heat of formation (kcal/mole)	distance oxygen anion to olefin (Å)	Δ (deprot.-prot.)
3	23.08	**42**	32.15	2.63	9.07
4	19.29	**43**	27.23	2.55[5]	7.94
12	-39.97	**44**	-32.09	2.55	7.90

products in this MERP-calculation. Their respective energies and the C-O bond lengths are collected in Table 4.2.

The MERP-calculations are carried out by gradually decreasing the distance between the oxygen anion and the nearest olefinic carbon in alcoholates **42**, **43** and **44**, followed by energy minimization (Table 4.3). The net atomic charges on the olefinic carbon and oxygen atoms are also calculated. Analysis of the data reveals that for all three starting alcoholates **42**, **43** and **44** the distance between the oxygen and carbon atom in the transition state is about 1.8 Å . At about that distance an energy optimum is calculated for all three substrates. A graphic representation of the energy profile for all three conversions is given figure 4.2. These profiles suggest that the transition state starting from alcoholate **42** is reached somewhat later than those starting from **43** and **44** and that the enthalpy of activation is approximately 2 kcal/mole higher than for **43** and even 4.5 kcal/mole more than for **44**. These differences in activation enthalpy are obviously not sufficient to explain the complete absence of any cyclization products when **3** is reacted with base. A determining

Table 4.2



45 Y=CH_2, m=0

46 Y=$(CH_2)_2$, m=0

47 Y=O, m=1

structure	heat of formation (kcal/mole)	distance oxygen atom to original olefinic C-atom (Å)
45	39.18	1.486
46	30.91	1.478
47	-29.69	1.494

factor may be the entropy of activation which by the term $T\Delta S^{\neq}$ may considerably contribute to the free energy of activation $\Delta G^{\neq}$. As both **3** and **4** are rather rigid structures it may be assumed that the entropy changes as the result of intramolecular ring closure in these polycycles are relatively small. In order to allow ring closure a more organized transition state will be necessary, therefore it is expected that $\Delta S^{\neq}$ will be negative and will enlarge the free energy of activation. Comparing structures **3** and **4**, and their corresponding alcoholates, the outbending effect of the C(8)-C(9) ethylene bridge in **4** and **43** causes the oxygen atom to be considerably closer to the olefinic bond than in **3** and **42**. This compression effect in **43** will certainly induce an increased interaction between both functionalities leading to a higher degree of organization around the future reaction center. As a consequence the entropy of activation for this addition reaction will be less negative for **43** than for **42**, therefore again favoring **43**. The diffence in activation entropy between **42** and **43** could not be determined, however the calculated reaction path shows that the oxygen anion in **42** has to move about 1.45Å to reach the transition state whereas for **43** a distance of only 1.25Å has to be covered (fig. 4.3). This calculated difference in distances suggests a difference in entropies of activation between these two alcoholates with the consequence that the difference in the corresponding free energies of activation for the reaction of **42** and **43** is sufficient to explain the complete blocking of the closure of **42**.

Finally, the MERP-calculations show that in the transition state there is a considerable development of negative charge on the carbon atom that is not involved in the bond formation (Table 4.3). This finding is in agreement with the mechanistic explanation for this base-induced intramolecular addition of an alcoholate to a non-activated alkene as given by Kirby[1] and Ganter[15].

Table 4.3

distance	energy	net atomic charge		
	(kcal/mole)	carbon 1*	carbon 2	oxygen
MERP-calculations for **42**				
2.600	32.17	-0.134	-0.143	-0.662
2.500	32.59	-0.114	-0.162	-0.663
2.400	33.60	-0.087	-0.189	-0.662
2.300	35.20	-0.055	-0.227	-0.658
2.200	37.20	-0.016	-0.278	-0.648
2.100	39.14	0.028	-0.344	-0.630
2.000	40.64	0.075	-0.426	-0.600
1.900	42.11	0.118	-0.517	-0.557
1.800	43.65	0.151	-0.606	-0.503
1.700	43.07	0.170	-0.684	-0.445
1.600	40.54	0.173	-0.743	-0.388
MERP-calculations for **43**				
2.100	32.45	0.018	-0.341	-0.622
2.000	33.80	0.066	-0.423	-0.594
1.900	35.80	0.111	-0.516	-0.553
1.800	37.08	0.146	-0.608	-0.500
1.700	35.37	0.166	-0.690	-0.442
1.600	32.50	0.172	-0.752	-0.386
MERP-calculations for **44**				
2.400	-31.45	-0.067	-0.211	-0.679
2.300	-30.58	-0.035	-0.253	-0.673
2.200	-29.28	0.000	-0.302	-0.662
2.100	-28.10	0.041	-0.366	-0.642
2.000	-27.20	0.083	-0.441	-0.611
1.900	-26.28	0.125	-0.532	-0.565
1.800	-24.88	0.155	-0.618	-0.510
1.700	-26.06	0.173	-0.692	-0.451

Figure 4.2 A graphic representation of the energy values for 3, 4 and 13

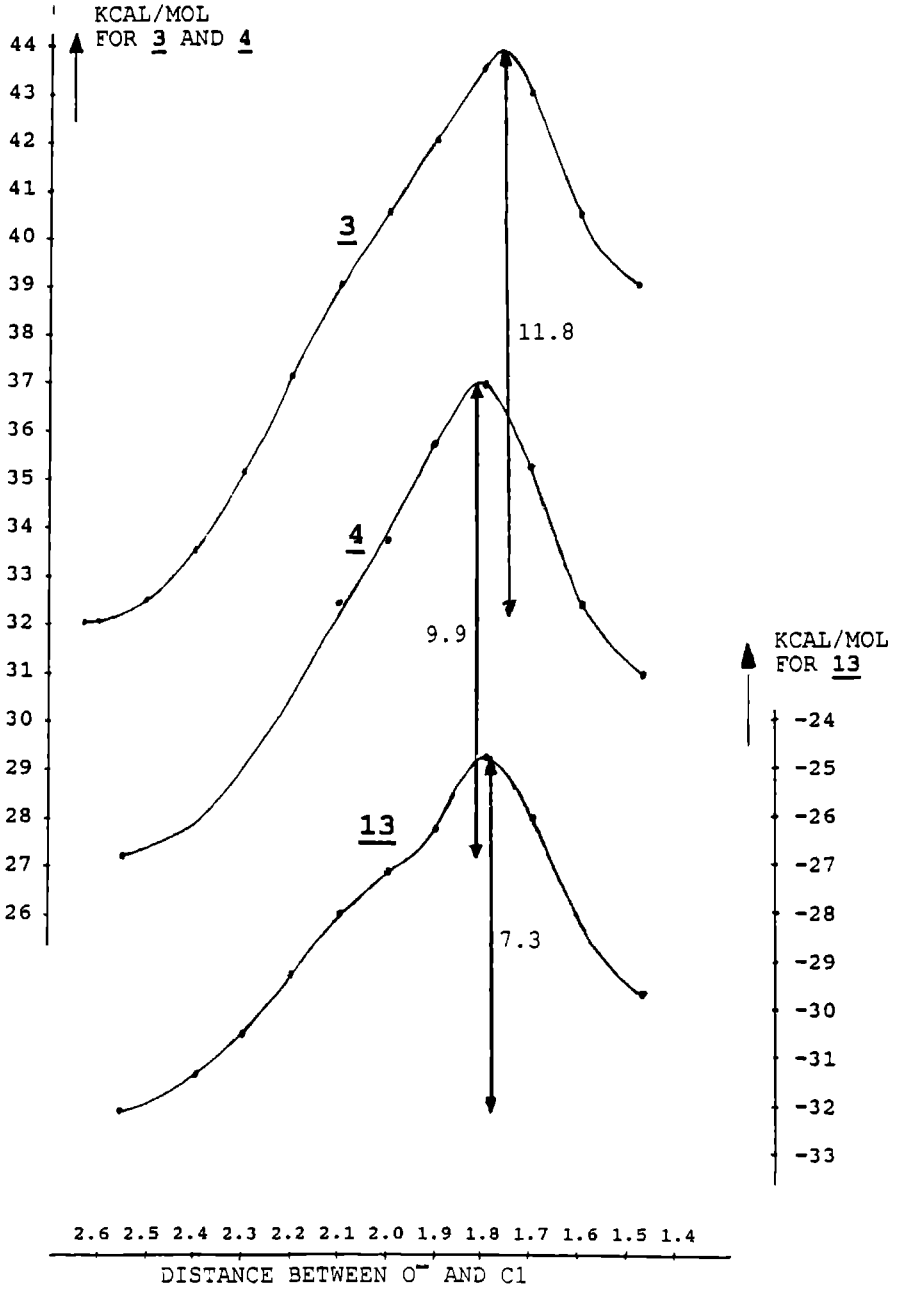
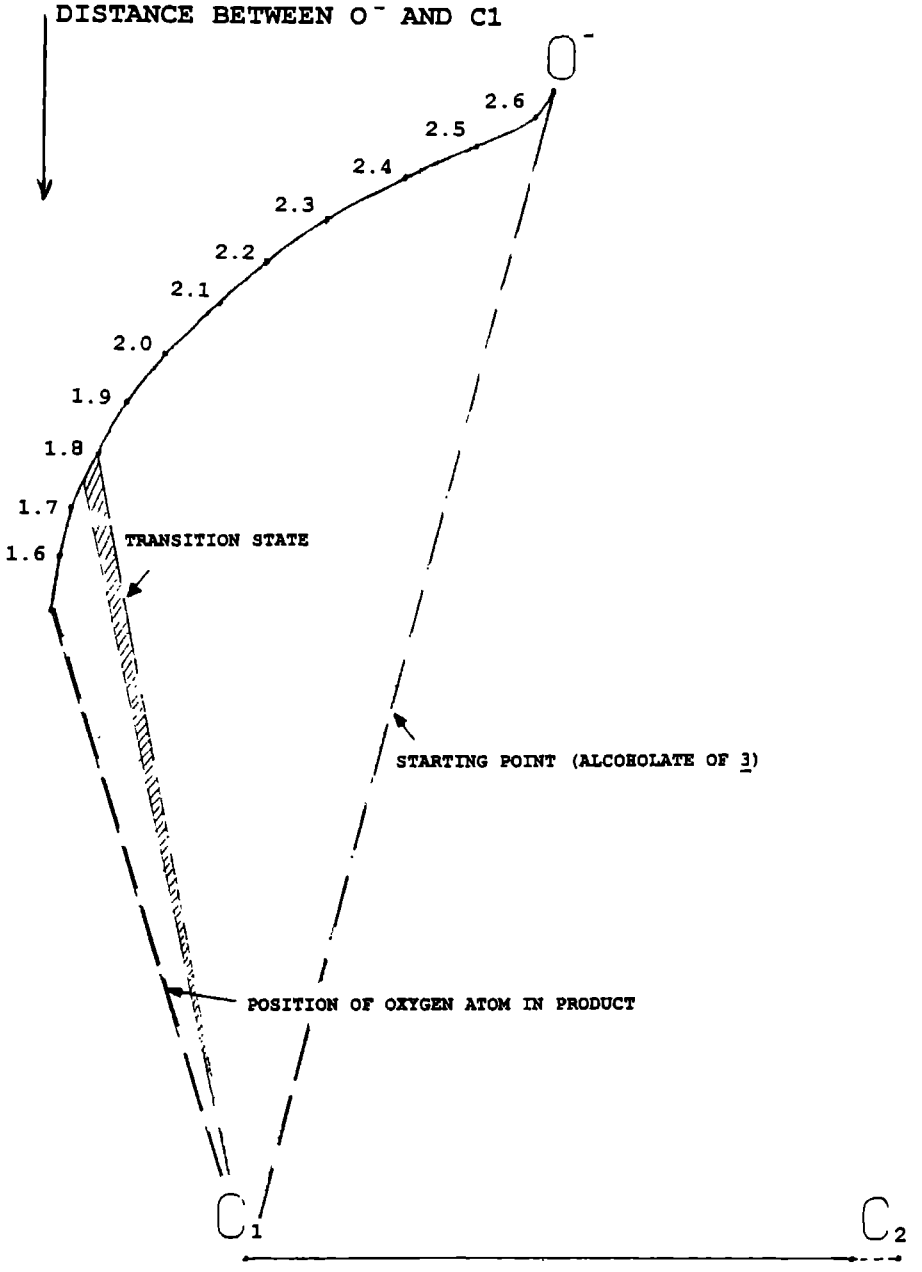


Figure 4.3 A graphic representation of the calculated route for the attack of the oxygen anion on the olefinic group of 3



4.5 Oxacage formation from 10-*endo*-2,9-methano-brend-4-ene-10-ol 3 by bromination.

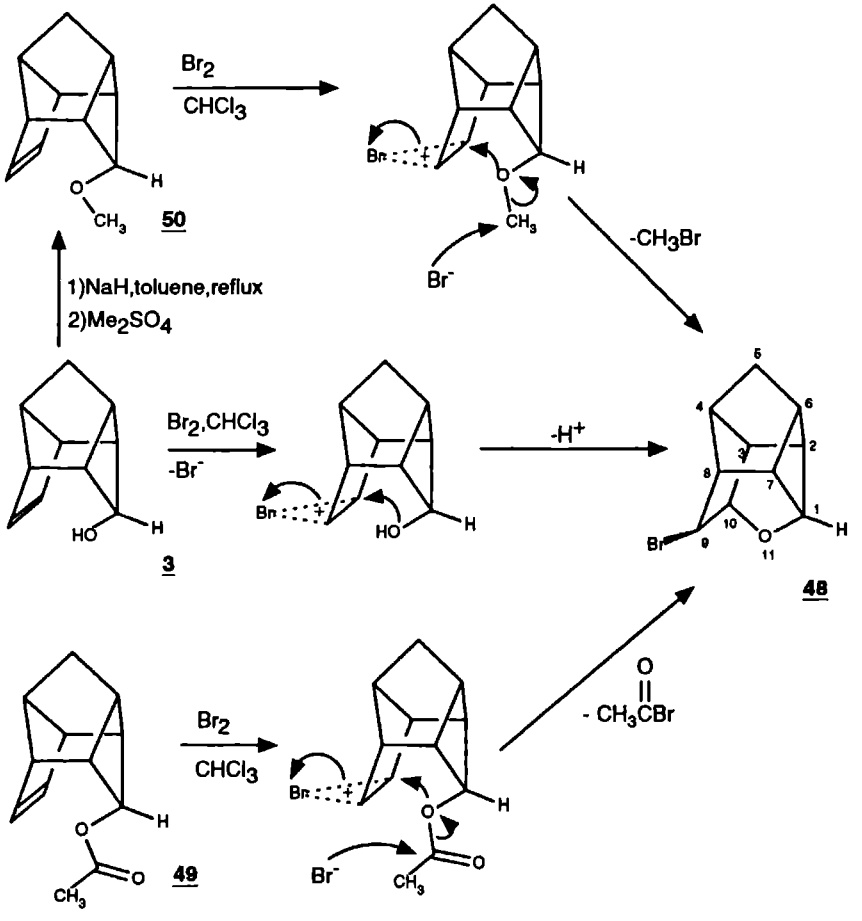
The failure of brendenol 3 to produce the corresponding oxacage compound on attempted base-induced intramolecular cyclization was a reason to investigate the possibility of a cage closure under electrophilic conditions. For this purpose the bromination of brendenol 3, its acetate 49 and its methyl ether 50 was studied with the objective to learn whether such activation of the alkene function in these compounds would lead to ether formation. It was argued that addition of bromine to the double bond at the sterically most favorable *exo*-face of 3 would produce a *exo*-bromonium ion which has the required spatial position with respect to the alcohol function to allow an intramolecular reaction. The strong electrophilic nature of such a bromonium ion would constitute the driving force for this reaction to occur. Treatment of brendenol 3 with bromine in chloroform gave a smooth reaction which afforded bromo ether 48 as a single product in high yield (Scheme 4.10). Its structure was secured by its spectral data. The mass-spectrum showed a M^+-peak of 226 with an ^{81}Br isotope peak at 228, which means that only one bromine atom is incorporated in the newly formed product 48. The IR and ^1H-NMR spectrum revealed the absence of an alcohol and olefinic function. The ^1H-NMR spectrum, however, showed three proton resonances between δ 4 and 5 ppm, which correspond to the two protons adjacent to the ether function (at C_1 and C_{10}) and the one proton adjoining the bromine atom (at C_9). The formation of 48 can be best explained, as already indicated above, by assuming initial bromination of the olefinic bond in 3 to form a bromonium ion that rapidly undergoes an intramolecular rear-side attack by the *endo*-alcohol function. The chemoselective high yield formation of 48 shows that the steric constraints for this reaction are apparently less severe than those in the direct nucleophilic reaction with the olefinic bond.

Surprisingly, acetate 49 also reacted rapidly with bromine in chloroform to give again 48 as the single product. It is assumed that the first step is again bromination of the olefinic bond followed by attack of the nucleophilic alkyl oxygen atom of the acetate ester on the bromonium ion. This leads to a considerable increase of electron deficiency at the carbonyl ester moiety which triggers bromide addition at this position. Elimination of the alkyl oxygen then results in the ultimate formation of acetyl bromide and cyclic ether 48. The unexpected ease of this cyclic ether formation starting from acetate 49 shows the high reactivity of the intermediate bromonium ion.

In order to establish whether such cyclic ether formation would also be possible for the corresponding alkyl ether, which is expected to be more stable under the reaction conditions, methyl ether 50 was prepared. Starting from brendenol 3 methyl ether 50 was obtained in 73% yield by reaction with sodium hydride in toluene at reflux temperature followed by the addition of dimethyl sulfate. When methyl ether 50 was subjected to reaction with bromine in chloroform a fast discoloration of the solution was observed. Work-up resulted again in the exclusive formation of the cyclic addition product 48 in 57% yield (Scheme 4.10). Clearly, this cyclic ether 48 can only be produced by methyl ether cleavage during the process. The mechanism proposed for this reaction is similar to that described for acetate 49. Because of the high reactivity of the bromonium ion and the

close proximity of methyl ether function initial overlap of a lone pair on the ether oxygen takes place activating the ether function in such a way that bromide attack at the methyl carbon accomplishes methyl oxygen bond cleavage leading to cyclic ether **48** and methyl bromide. This observation of an extremely facile methyl ether cleavage in **50** is another illustration of the importance of close proximity for the chemical interaction of two functional groups constrained in rigid polycyclic systems. Activation of one of these functions *e.g.* by deprotonation of alcohol **4** or by bromination of **50** leads to unanticipated results, *viz.* addition of an alcoholate to a non-activated double bond to give **29** or demethylation of a methyl ether with concomitent formation of oxacage compound **48**.

Scheme 4.10



For general remarks, see section 2.4

Tricyclo[5.3.1.$0^{3,7}$]non-4-ene-9-methanol (**27**)

3 (100 mg, 0.68 mmol) was added to a 1 M KOtBu solution in tBuOH (5 ml). After 14 h. of stirring at 80°C under a N_2-atmosphere diethyl ether (25 ml) and water (15 ml) were added. The water layer was neutralised with 3% aqueous HCl. Then, the organic layer was washed with water (5 ml) and with saturated aqeous $NaHCO_3$ (5 ml), dried ($MgSO_4$) and concentrated *in vacuo*, to give **1** and **27** (80 mg, 48:52 acc. GLC, 98%) as a light yelow oil. Purification with flash chromatography (silica gel, EtOAc/n-hexane = 3/1) resulted in pure **27** (38 mg, 0.25 mmol, 37%) as a yellow oil and pure **1** (37 mg, 0.25 mmol, 38%) as a white solid.

IR (CCl_4) v: 3620 + 3560-3300 (-OH), 3050 (s, -CH unsat.), 2950 + 2860 (-CH sat.) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 90 MHz) δ: 5.95 (s, 2H, olefine), 3.1 (m, 1H), 2.5-2.2 (m, 5H), 2.0 (m, 2H), 1.65 (md, 2H), 1.4 (md, 2H) ppm. GCMS m/e: 150 (M^+, 32.7%), 132 (-H_2O, 7.8%), 117 (-CH_3OH, 40.9%), 106 (-CH-CH_2OH, 19%), 91 (70.7%), 79 (100%). EI/HRMS m/e: Found: 150.1052 amu (Calc for $C_{10}H_{14}O$: 150.1045 amu).

4-Oxapentacyclo[6.4.0.0^{3,7}.0^{5,12}.0^{6,11}]dodecane (**29**)

A solution of **3** (80 mg, 0.49 mmol) containing one pellet of KOH in MeOH (10 ml) was heated at reflux for 24 h. After cooling to r.t. diethyl ether (40 ml) and water (10 ml) were added. The organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 5 ml), dried ($MgSO_4$) and concentrated *in vacuo*, to give **29** (47 mg, 0.29 mmol, 59%) as a light yellow oil.

IR (CCl_4) v: 2930 +2860 (s, -CH sat.) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 4.75 (t, 1H, >CH-O), 4.29 (t, 1H, >CH-O), 2.58 (m, 1H), 2.40 (m, 1H), 2.17 (m, 2H), 1.85-1.35 (m, 8H) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 83.4 (tert, >CH-O), 80.6 (tert, >CH-O), 45.1 (tert), 42.5 (tert), 40.9 (tert), 38.9 (tert), 38.8 (sec), 37.9 (tert), 23.3 (tert), 19.9 (sec), 16.2 (sec) ppm. CI/MS m/e: 163 (M^++1, 42%), 162 (M^+, 28%), 161 (-H^+, 32%), 145 (-OH, 72%), 135 (29%), 119 (100%), 117 (49%), 91 (43%). EI/HRMS m/e: Found: 162.1049 (Calc. for $C_{11}H_{14}O$ (M^+): 162.1045)

5-Methyl-4-oxapentacyclo[6.4.0.0^{3,7}.0^{5,12}.0^{6,11}]dodecane (**30**)

A solution of **6** (120 mg, 0.68 mmol) in MeOH (5 ml) and a 4 N aqueous NaOH solution (5 ml) were heated to reflux for 3 h. After cooling to r.t. diethyl ether (40 ml) and water (10 ml) were added. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution (2 × 5 ml), dried ($MgSO_4$) and concentrated *in vacuo*, to give **30** (106 mg, 0.60 mmol, 88%) as a clear colorless oil (purity (GLC): 94%).

IR (CCl_4) v: 2930 +2860 (s, -CH sat.) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 4.66 (dt, 1H, >CH-O), 2.66 (m, 1H), 2.19 (m, 1H), 2.06 (dt, 1H), 1.91 (dd, 1H), 1.76 (m, 2H), 1.69 (d, 1H), 1.61 (m, 3H),

1.44 (m, 1H), 1.41 (m, 1H(D)), 1.36 (s, 3H) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 85.9 (quat, C-O), 81.6 (tert, >CH-O), 47.0 (tert), 45.2 (tert), 43.9 (tert), 40.4 (tert), 39.0 (sec), 38.0 (tert), 24.6 (tert), 19.6 (prim), 19.4 (sec), 16.2 (sec) ppm. CI/MS m/e: 177 (M^++1, 46%), 176 (M^+, 100%), 159 (-H_2O, 21%), 133 (22%), 118 (14%), 95 (40%). EI/HRMS m/e: Found: 176.1229 (Calc. for $C_{12}H_{16}O$ (M^+): 176.1223).

5-Butyl-4-oxapentacyclo[6.4.0.0^{3,7}.0^{5,12}.0^{6,11}]dodecane (**31**)

a) A solution of **8** (176 mg, 0.81 mmol) in 6 ml MeOH containing 6 ml of a 4 N NaOH solution was heated at reflux (85°C) for 3 h. After cooling to r.t. ether (40 ml) and water (10 ml) were added. The two layers were separated and the organic layer was washed with a saturated $NaHCO_3$ solution (2 × 5 ml). Then the organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*, to give **31** (162 mg, 0.74 mmol, 92%) as a clear colorless oil (purity (GLC): 92%).

b) A solution of **8** (176 mg, 0.81 mmol) in MeOH (10 ml) containing 1 pellet of KOH was heated at reflux for 1 h. After cooling to r.t. diethyl ether (40 ml) and water (10 ml) were added. The organic layer was washed with an aqueous saturated $NaHCO_3$ solution (2 × 5 ml), dried ($MgSO_4$) and concentrated *in vacuo*, to give **31** (162 mg, 0.74 mmol, 92%) as a light yellow oil.

IR (CCl_4) v: 2930 +2860 (s, -CH sat.) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 4.65 (dt, 1H, >CH-O), 2.64 (m, 1H), 2.19 (m, 1H), 2.12 (dt, 1H), 1.96 (q, 1H), 1.80-1.25 (m, 14H), 0.9 (t, 3H) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 88.8 (quat, C-O), 81.5 (tert, >CH-O), 46.9 (tert), 43.6 (tert), 42.7 (tert), 40.6 (tert), 39.0 (sec), 38.1 (tert), 32.6 (sec), 26.5 (sec), 24.8 (tert), 23.2 (sec), 19.6 (sec), 16.3 (sec), 14.1 (prim) ppm. CI/MS m/e: 219 (M^++1, 6%), 218 (M^+, 21%), 135 (16%), 133 (17%), 85 (25%), 84 (21%), 83 (30%). EI/HRMS m/e: Found: 218.1666 (Calc. for $C_{15}H_{22}O$ (M^+): 218.1671)

5-Phenyl-4-oxapentacyclo[6.4.0.0^{3,7}.0^{5,12}.0^{6,11}]dodecane (**32**)

A solution of **10** (80 mg, 0.34 mmol) in MeOH (6 ml) containing 1 pellet of KOH was heated at reflux for 20 min. After cooling to r.t. diethyl ether (40 ml) and water (10 ml) were added. The organic layer was washed with an aqueous saturated $NaHCO_3$ solution (2 × 5 ml), dried ($MgSO_4$) and concentrated *in vacuo*, to give **32** (76 mg, 0.32 mmol, 95%) as a clear colorless oil (purity (GLC): 93%).

IR (CCl_4) v: 2930, 2860 (s, -CH sat.), 700 (s, -CH arom.) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 7.45 (m, 2H, CH arom.), 7.34 (t, 2H, CH arom.), 7.27 (t, 1H, CH arom.), 4.83 (dt, 1H, >CH-O), 2.82 (m, 1H), 2.64 (dt, 1H), 2.48 (q, 1H), 2.37 (m, 1H), 1.86 (d, 1H), 1.83-1.70 (m, 3H), 1.68-1.48 (m, 3H), 1.45-1.35 (m, 1H) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 139.9 (quat, 1C, >C(O)C (of phenyl ring)), 128.1 (tert, 2C, C(arom.)), 127.5 (tert, 1C, C(arom.)), 126.9 (tert, 2C, C(arom.)), 89.4 (quat, 1C, >C(O)C (of phenyl ring)), 82.7 (tert, 1C, >CH-O), 46.8 (tert, 1C), 44.7 (tert, 1C), 42.8 (tert, 1C), 40.5 (tert, 1C), 38.9 (sec, 1C), 23.7 (tert, 1C), 19.3 (sec, 1C), 16.0 (sec, 1C) ppm. CI/MS m/e: 239 (M^++1, 74%), 238 (M^+, -H^+, 100%), 237 (-H_2, 36%), 221 (-H_2O, 43%), 195 (40%), 157 (76%), 119 (69%), 105 (63%), 91 (32%). EI/HRMS m/e: Found: 238.1360 (Calc. for $C_{17}H_{18}O$ (M^+): 238.1358 amu.

3-Bromo-5-oxapentacyclo[5.4.0.0^{2,9}.0^{4,8}.0^{7,11}]undecane (**48**)

a) Reaction of **3** with bromine: To a solution of **3** (200 mg, 1.35 mmol) in $CHCl_3$ (10 ml) was added a solution of Br_2 (240 mg, 1.5 mmol) in $CHCl_3$ (15 ml). The resulting mixture was stirred for 0.5 h, then CH_2Cl_2 (25 ml) was added. The organic reaction mixture was washed with 1N aqueous KOH solution (15 ml) and saturated NaCl solution (15 ml), dried ($MgSO_4$) and concentrated *in vacuo*, to give **48** (290 mg, 1.28 mmol, 95%) as a light yellow oil.

b) Reaction of **49** with bromine: The same procedure as used for **3** in the synthesis of **48** was applied to **49** (175 mg, 0.92 mmol), using Br_2 (160 mg, 1.0 mmol) dissolved in $CHCl_3$ (10 ml), to give **48** (196 mg, 0.86 mmol, 94%) as a clear and colorless oil.

c) Reaction of **50** with bromine: The same procedure as used for **3** and **49** in the synthesis of **48** was applied to **50** (100 mg, 0.62 mmol), using Br_2 (120 mg, 0.75 mmol) dissolved in $CHCl_3$ (10 ml), to give a brown oil (184 mg). This oil was purified with flash-chromatography (silicagel; n-hexane/EtOAc=2/1), to give **48** (80 mg, 0.35 mmol, 57%) as a colorless oil.

IR (CCl_4) ν: 3000-2850 (-CH sat.), 1065-1030 (C-O) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 90MHz) δ: 4.7 (dd, 1H, H_9), 4.5 (s, 1H, H_{10}), 4.25 (t, 1H, H_1), 3.2 (m, 1H), 3.1-2.65 (m, 2H), 2.65-2.3 (m, 3H), 1.8 (s, 2H, bridge) ppm. EI/MS m/e: 228 (M^+(^{81}Br), 0.7%), 226 (M^+(^{79}Br), 0.7%), 147 (-Br, 51.5%), 117 (26.4%), 105 (100%), 91 (55.6%), 81 (62.6%). EI/HRMS m/e: Found: 225.9998 (Calc. for $C_{10}H_{11}OBr$ (M^+(^{79}Br)): 225.9993).

3-endo-Methoxy-tetracyclo[5.3.0.0^{2,5}.0^{4,8}]deca-9-ene (**50**)

To a suspension of NaH (36 mg, 1.5 mmol) in toluene (10 ml, sodium-dried) a solution of **3** (150 mg, 1.01 mmol) in toluene (5 ml, sodium-dried) was added. The mixture was heated at reflux and stirred for 6 h, then Me_2SO_4 (630 mg, 5 mmol) was added very quickly at the still warm solution. The reaction mixture obtained was stirred for another 0.5 h, then washed with a 3% aqueous HCl solution (5 ml), dried ($MgSO_4$) and concentrated *in vacuo*, to give a light yellow oil (161 mg). This oil was purified using flash chromatography (silicagel; n-hexane/ EtOAc=5/1), to give **50** (120 mg, 0.74 mmol, 73%) as a clear colorless oil.

IR (CCl_4) ν: 3060 (-CH unsat.), 3000-2850 (-CH sat.), 1130 (C-O) cm^{-1}. ^{1}H-NMR ($CDCl_3$; 400MHz) δ: 6.09 (s, 2H, olefin), 3.87 (dt, 1H, -C<u>H</u>OCH$_3$), 3.10 (d, 3H, -CHOC<u>H</u>$_3$), 2.96 (m, 1H), 2.58 (dt, 2H), 2.46 (m, 3H), 1.62 (s, 2H, bridge) ppm. ^{13}C-NMR ($CDCl_3$; 100MHz) δ: 136.3 (tert, 2C, olefine), 78.5 (tert, 1C, -<u>C</u>(H)OCH$_3$), 66.3 (tert, 1C), 54.4 (prim, 1C, -C(H)O<u>C</u>H$_3$), 48.1 (tert, 2C), 45.2 (tert, 3C), 32.8 (sec, 1C, bridge) ppm.

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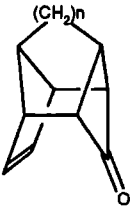
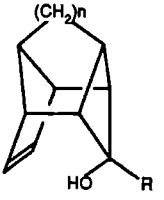
This thesis deals with the synthesis of carbonyl-brendenes 1-3 and describes some of their chemical properties. Furthermore, attention is given to strained *endo*-alkenols 4 and 5 which are of interest as models for the study of nucleophilic addition to non-activated olefins. These half cage systems 1-3 are unique structures as they are highly strained and contain two π-systems in close proximity constrained in a rigid framework. The impact of these structural features on the chemical reactivity of carbonylbrendenes 1 and 2 and the corresponding alcohols 4 and 5 is the main topic of this thesis.



1 n=1
2 n=2
3 n=3



4 n=1
5 n=2

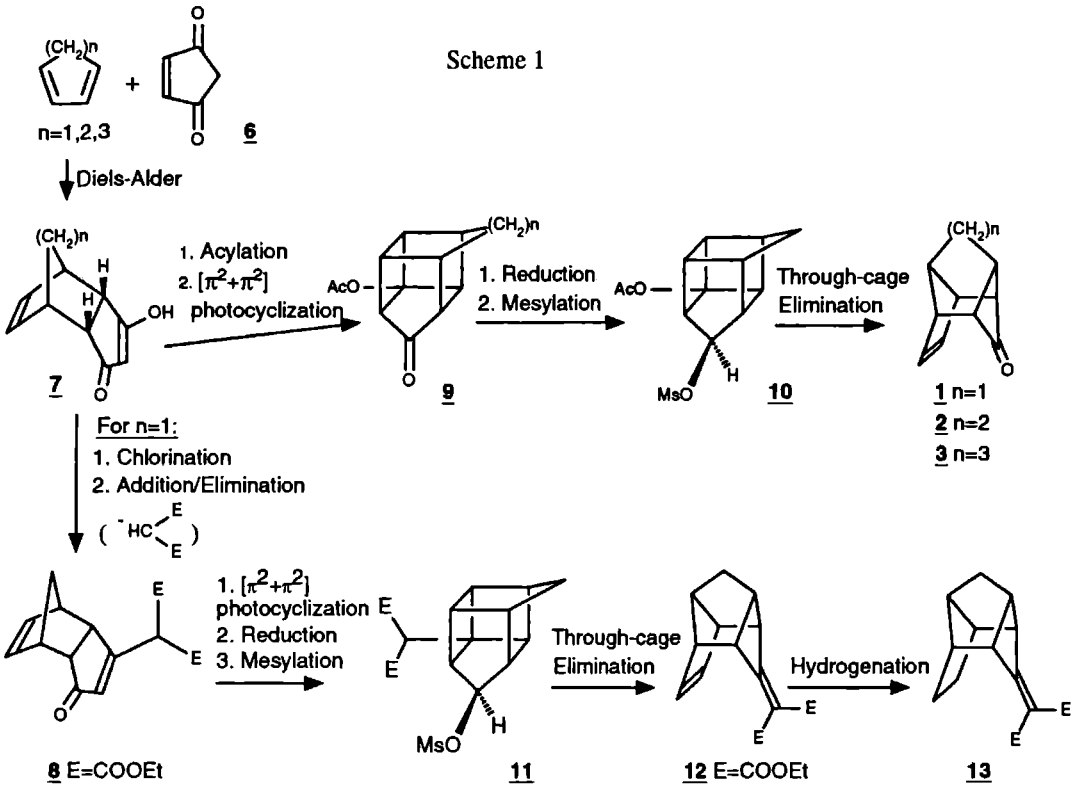
Chapter 1 describes the principle of homo-enolization/homoketonization and gives a historical overview of the base-induced cage opening in cubane-type alcohols, which is the basis for the synthesis of tetracyclic enones 1-3. Furthermore, the IUPAC nomenclature rules relevant for the polycyclic structures treated in this thesis are explained as well as their trivial names which are used in the text.

In Chapter 2 the syntheses of tetracyclic enones 1-3 and methylidene derivative 12, are described (Scheme 1). All these half-cage structures are accessible by applying three principal steps: (i) synthesis of an appropriately substituted precursor, the so-called photoprecursor; (ii) subsequent $[\pi^2+\pi^2]$-photocyclization of the photoprecursor to form the basic cage skeleton; (iii) modification of the cage compound thus obtained to give the desired polycyclic structure.

Photoprecursors 7 (n= 1,2,3) are accessible by the Diels-Alder reaction of cyclopentadiene, cyclohexadiene or cycloheptadiene with cyclopentene-1,4-dione 6. Whereas tricyclodecadienones 7 for n=1 and 2 are readily obtained in high yields, employment of high pressure (15 kbar) appeared essential for the formation of the n=3 homolog. Even under this high pressure condition only modest yields (≤30%) were obtained for 7 (n=3). The photoprecursor 8, needed for the synthesis of 12, was prepared starting from 7 (n=1) by conjugate addition of a diethyl malonate anion to the corresponding β-chloroenone.

The intramolecular photochemical $(\pi^2+\pi^2)$ cage closure of the photoprecursors 7 to give the corresponding 1,3-bishomocubanone derivatives 9 was realized in high yields using the enol acetates of 7. Access to half cage enones 1-3 was obtained by stereoselective reduction of the ketone moiety

Scheme 1



in 9 followed by mesylation to the mesylates 10 and subsequent treatment with sodium methoxide in methanol. In this last reaction an effective through-cage elimination takes place leading to the desired enones in high yields. In a similar way mesylate 11 was prepared from 8 and transformed into diene 12.

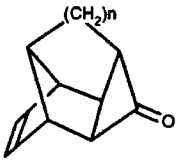
The spectroscopic features of 1, 2 and 3 strongly suggest non-bonded interactions between the carbonyl and olefinic function. Convincing evidence for the nature of this electronic interaction was derived from the spectroscopic properties of 12. A pertinent charge-transfer band at 255 nm was observed in its UV-spectrum. Such an absorption is absent in the UV-spectrum of its saturated analogue 13.

In Chapter 3 the chemical behavior of the carbonyl-brendenes 1 and 2 is described. It is shown that the carbonyl-brendenes 1 and 2 are highly reactive compounds which, under a variety of both Brönsted and Lewis acid conditions, rapidly rearrange to thermodynamically more stable products such as the carbonyl-brexenes 14 and 15. The use of nucleophilic acids leads to the formation of tricyclic enones 16 in which the nucleophile is incorporated into the product. Relief of strain energy is the principal driving force for these isomerization processes which in essence are cyclobutyl/cyclopropyl carbinyl rearrangements. Due to their lability toward acidic reagents nucleophilic additions to the carbonyl function in both 1 and 2, which require the use of an acidic

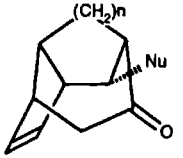
catalyst or an acidic reagent, could not be accomplished. A striking example is the addition of Grignard reagents to both 1 and 2 which, quite unexpectedly, did not give the anticipated addition at the cyclobutanone carbonyl function but instead led to complete isomerization to 14 and 15, respectively. The Lewis-acidity of Grignard reagents is apparently strong enough to induce a rearrangement in these enones. Using the less coordinating organolithio reagents no rearrangement was observed. Instead high yields of the expected *endo* alcohols 4 and 5 were obtained. These alcohols show intramolecular hydrogen bonding between the hydroxy group and the alkene function as the result of their close proximity. Attempts to reduce 1 applying lithium in ammonia led to tricyclic alcohol 17 via a radical anion which rapidly undergoes ring cleavage to form a stable allylic radical with considerable release of ring strain. Reaction of 1 and 2 with amines to produce imines under neutral or slightly basic conditions did not meet with success. Enone 1 did not react at all, while for 2, with hydrazine as the amine, a remarkable bond cleavage reaction to bicyclic hydrazide 18 was observed. Interestingly, the Wittig olefination using methylenetriphenylphosphorane was successful for 1 but failed completely for 2. The rather long reaction time needed for this conversion of 1 into diene 19 shows again the reluctance of the cyclobutanone carbonyl function to undergo nucleophilic additions. All these experimental results indicate a surprisingly low reactivity of the cyclobutanone carbonyl function toward nucleophilic additions in both 1 and 2. Structural features of steric and electronic nature, may be responsible for this unusual behavior.

Some insight into the chemical reactivity of the olefinic double bond in 1 and 2 was obtained by subjecting these compounds to typical olefinic reactions such as hydrogenation, bromination and a 1,3-dipolar cycloaddition with diazomethane. Hydrogenation of the double bond in 1 to 20 without the occurrence of skeletal rearrangement could only be accomplished in the presence of some amine. Without amine almost quantitative rearrangement to the carbonyl-brexene system occurred prior to hydrogenation. Bromination of both 1 and 2 in chloroform led only to complex mixtures of products from which no identifiable structure could be isolated. It was shown however, that rearrangement of 1 and 2 to the corresponding carbonyl-brexenes is a major pathway in this halogenation reaction. A unique cyclopropyl containing lactone 21 was obtained from the bromination reaction of 2 in tetrachloromethane. Such a lactone was not observed for 1. Finally, diazomethane addition to 1, 2 and their corresponding alcohols and acetates leads to products 22. A distinct effect of the carbonyl function on the reactivity of the olefinic double bond in these cycloadditions was established. The higher reactivity of the carbonyl-brendenes 1 and 2 toward diazomethane as compared with the corresponding alcohols and acetates is explained by assuming non-bonded interaction between the two π-functions creating a 'pseudo-enone' moiety in 1 and 2.

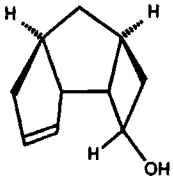
Chapter 4 is devoted to the chemistry of strained alkenols 4 and 5. These alcohols are particular interesting as they possess a hydroxylic and an olefinic function in close proximity. Intramolecular addition of the alcohol oxygen to the non-activated double C-C bond was investigated. Attempts to induce such an intramolecular nucleophilic addition both under neutral and basic conditions (sodium methoxide in methanol) failed for 4. When a stronger base was used such as potassium t-butoxide in t-butyl alcohol alkenol 4 (for R=H) underwent a cyclobutanone ring



14 n=1
15 n=2



16 Nu = Cl and n = 1
Nu = Br and n = 1,2
Nu = OMe and n = 2



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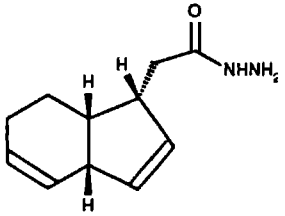

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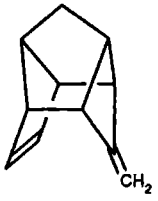

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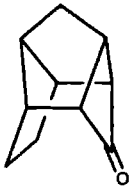

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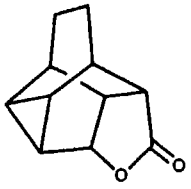

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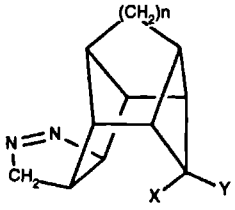
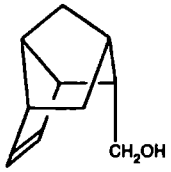
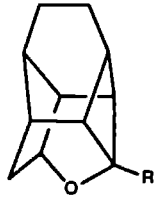


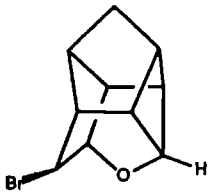
22 X=Y=O; n=1,2
X=OH, Y=H; n=1,2
X=OAC, Y=H, n=1,2

opening to give enone **1** and carbinol **23**. An entirely different behavior was observed for alkenols **5**. Using sodium methoxide in methanol at reflux temperature a smooth formation of oxacage compounds **24** was observed. A more detailed study of this addition reaction revealed that the use of a protic solvent is essential. The mechanism involves a reversible deprotonation of the alcohol function followed by the rate determining addition of the alcoholate anion to the olefinic double bond forming a carbanion-like transition state with participation of the protic solvent disposed at the *exo* face of the molecule. The occurrence of stereospecific *exo* protonation was demonstrated by a D-labeling experiment. The observation that the tertiary alkenols **5** (R≠H) react faster than secondary alkenol **5** (R= H) is rationalized by the increasing compression of the former alkenols as the results of stronger pyrimidalization of the carbinol carbon. The inreactivity of alkenols **4** is explained by their higher rigidity resulting in a higher enthalpy of activation as has been confirmed by Minimum Energy Reaction Path-calculations. Intramolecular addition of the hydroxylic function to the olefinic center could be realized in **4** (R=H) by activation of the double bond by bromination. The formation of a bromonium ion in close proximity to the alcohol function leads to the fast formation of oxacage compound **25**. This activation is so powerful that even the methyl ether of **4** (R= H) is rapidly converted into **25**.

In conclusion, tetracyclic enones **1-3** constitute intriguing structures the chemistry of which is typically associated with their strained and rigid structures having two π-systems in close proximity. The cyclobutanone moiety is extremely sensitive to both Brönsted and Lewis acids and rapidly



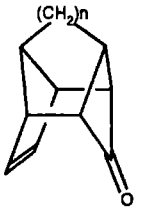




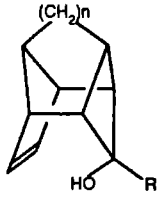
23 **24** R = H, Me, n-Bu, Ph **25**

rearranges via a cyclobutyl/cyclopropylcarbinyl/homoallylic cation intermediate to more relaxed structures. In addition the cyclobutanone carbonyl function show an unexpected low reactivity toward nucleophilic addition reactions. Tetracyclic alcohols **4** and **5** are excellent model compounds to gather fundamental insight in the addition of nucleophiles to non-activated olefinic bonds. It was shown that proximity effects and rigidity of the molecule play a crucial role in this type of reactions.

In dit proefschrift worden de resultaten van een onderzoek over de synthese en chemische eigenschappen van de carbonyl-brendenen **1**-**3** beschreven. Tevens, wordt aandacht besteed aan de gespannen *endo*-alkoholen **4** en **5**, met name aan de intramoleculaire nucleofiele additie aan de niet-geactiveerde olefine-functie. De halfkooi-systemen **1**-**3** zijn unieke structuren, omdat zij een hoge spanningsenergie hebben en twee dichtbij elkaar geplaatste π-systemen in een star koolstofskelet. De invloed van deze structurele eigenschappen op de chemische reactiviteit van de carbonyl-brendenen **1** en **2** en de hiervan afgeleide alkoholen **4** en **5** vormt de rode draad in dit proefschrift.



1 n=1
2 n=2
3 n=3



4 n=1
5 n=2

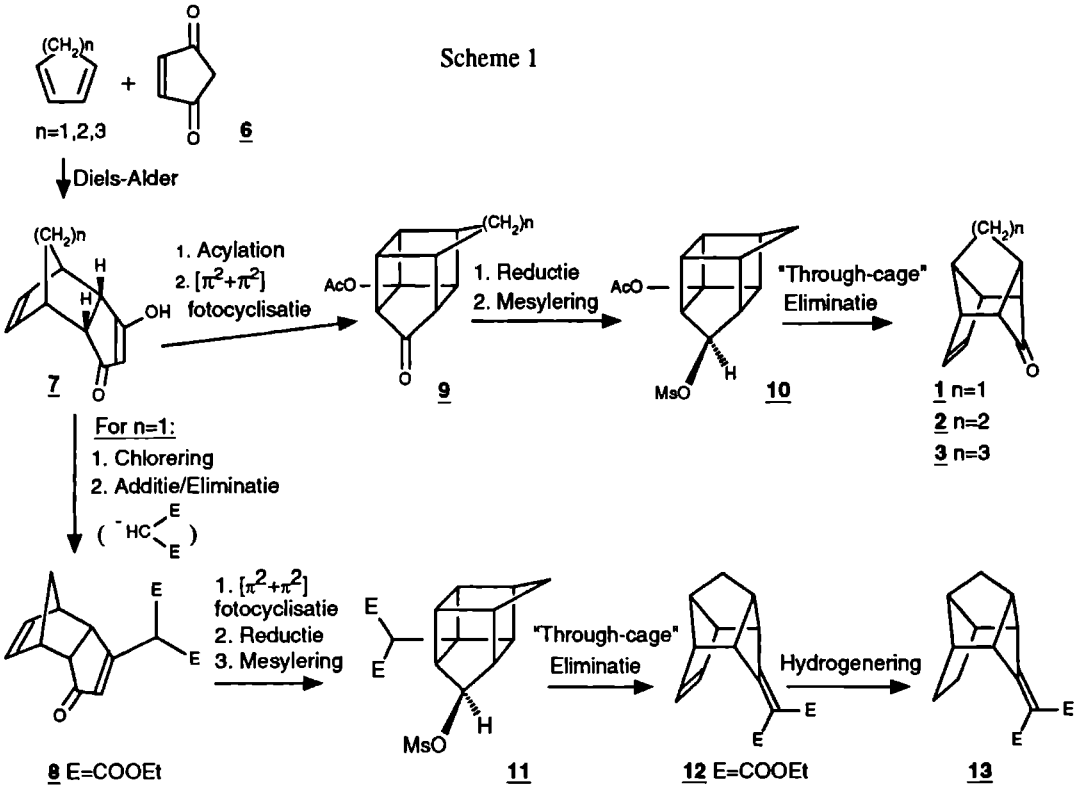
Hoofdstuk 1 beschrijft het principe van de homo-enolisatie/homoketonisatie en geeft een historisch overzicht van de base-geïnduceerde kooi-opening aan kubaan gerelateerde alkoholen, die de grondslag vormt voor de synthese van de tetracyclische enonen **1**-**3**. Verder worden de regels van de IUPAC nomenclatuur relevant voor de polycyclische structuren, beschreven in dit proefschrift, besproken, alsmede de triviale namen voor deze systemen die in de tekst worden gebruikt.

In hoofdstuk 2 wordt de synthese van de tetracyclische enonen **1**-**3** en het methylideen derivaat **12** beschreven (Schema 1). Deze halfkooi-structuren kunnen worden verkregen door gebruik te maken van de volgende drie hoofdstappen: (i) synthese van een geschikt gesubstitueerde precursor, de zgn. fotoprecursor; (ii) daaropvolgende ($\pi^2+\pi^2$)-fotocyclisatie van de fotoprecursor tot het kooiskelet; (iii) modificatie van de verkregen kooiverbinding tot het gewenste polycyclische systeem.

De fotoprecursors **7** werden verkregen d.m.v. een Diels-Alder-reactie van cyclopentadiëen, cyclohexadiëen of cycloheptadiëen met cyclopenteen-1,4-dion **6**. Terwijl de tricyclodecadienonen **7** voor n=1 en n=2 relatief eenvoudig in hoge opbrengsten konden worden verkregen, bleek voor de vorming van de n=3 homoloog hoge druk (15 kbar) noodzakelijk te zijn. Zelfs bij deze hoge druk werden bescheiden opbrengsten (≤ 30%) voor **7** (n=3) verkregen. De fotoprecursor **8**, nodig voor de synthese van **12**, kon worden gesynthetiseerd d.m.v. een 1,4-additie van het diethyl-malonaat anion aan het overeenkomstige β-chloorenon van **7** (n=1).

De intramoleculaire fotochemische ($\pi^2+\pi^2$) kooisluiting van de fotoprecursors **7** tot de

Scheme 1

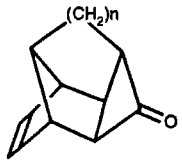


corresponderende 1,3-bishomokubanon-derivaten **9** kon in hoge opbrengsten worden gerealiseerd door uit te gaan van de enolacetaten van **7**. De kooi-enonen **1**-**3** konden vervolgens worden verkregen d.m.v. een stereoselectieve reduktie van de ketonfunctie in **9** gevolgd door een mesylering tot de mesylaten **10** en een reactie met natriummethoxide in methanol. In deze laatste reactie vindt in hoge opbrengst een effectieve "through-cage" eliminatie plaats tot de gewenste enonen **1**-**3**. Op een vergelijkbare manier werd uitgaande van **8** mesylaat **11** gesynthetiseerd en omgezet in diëen **12**.
De spectroscopische kenmerken van **1**,**2** en **3** duiden sterk op "non-bonded" interacties tussen de carbonyl en de olefine functie. Een overtuigend bewijs voor deze electronische interactie kon worden afgeleid uit de specroscopische gegevens van **12**. In het UV-spectrum van deze verbinding werd een "charge-transfer" absorptie bij 255 nm waargenomen. Een gelijksoortige absorptie was afwezig in het UV-spectrum van de overeenkomstige selectief gehydrogeneerde verbinding **13**.

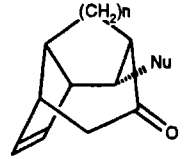
In hoofdstuk 3 wordt het chemisch gedrag van de carbonyl-brendenen **1** en **2** beschreven. Aangetoond werd dat de carbonyl-brendenen **1** en **2** hoogreactieve verbindingen zijn die, onder verschillende Brönsted- en Lewis-zure condities, snel omleggen tot thermodynamisch stabielere produkten, zoals de carbonyl-brexenen **14** en **15**. Het gebruik van nucleofiele zuren leidde tot de vorming van de tricyclische enonen **16**, waarbij het nucleofiel werd ingebouwd in het product. Verlaging van de spanningsenergie is de drijvende kracht achter deze isomerizatie processen, die in

feite cyclobutyl/cyclopropyl-carbinyl-kation- omleggingen zijn. T.g.v. hun labiliteit in de aanwezigheid van zure reagentia, konden nucleofiele addities aan de carbonylfunctie van 1 en 2, waarbij een zure katalysator of een zuur reagens nodig is, niet worden gerealiseerd. Een opvallend voorbeeld is de additie van Grignard reagentia aan 1 en 2. Nogal onverwacht leidde deze reactie tot een complete isomerisatie tot respectievelijk 14 en 15 en niet tot de verwachte additie aan de cyclobutanon-carbonylfunctie. Het Lewis-zure karakter van de Grignard reagentia is blijkbaar voldoende om een omlegging bij deze enonen te veroorzaken. Wanneer gebruik werd gemaakt van de minder coördinerende organolithium reagentia werd er geen omlegging waargenomen. In plaats daarvan werden in hoge opbrengsten de verwachte *endo*-alkoholen 4 en 5 verkregen. Deze vertonen een intramoleculaire waterstofbinding tussen de hydroxy-groep en de alkeen-functie als gevolg van hun dichte nabijheid. Pogingen om 1 met lithium in ammonia te reduceren leidde tot tricyclisch alcohol 17 via een radikaal anion, dat snel een ringopening ondergaat om een stabiel allylisch radikaal te vormen met een behoorlijke verlaging van de ringspanning. Reacties van 1 en 2 met amines onder neutrale of licht basische condities, met het doel imines te synthetiseren, leverde niet het verwachte resultaat op. Verbinding 1 vertoonde helemaal geen reactie, terwijl voor 2, met hydrazine als amine, een opvallende ontleding tot het hydrazide 18 werd waargenomen. Opvallenderwijs was de Wittig reactie van 1 met methyleentriphenylphosphoraan succesvol, maar met 2 totaal niet. De relatief lange reactietijd nodig voor de omzetting van 1 in 19 klopt wederom met het inreactieve karakter van de cyclobutanon carbonyl functie bij nucleofiele addities. Bij al deze experimenten is er sprake van een opvallend lage reactiviteit van de cyclobutanon carbonyl functie van 1 en 2 bij nucleofiele addities. Structurele eigenschappen van zowel sterische en electronische oorsprong, zouden verantwoordelijk kunnen zijn voor dit ongewone gedrag.

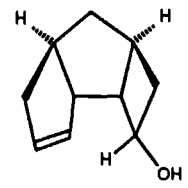
Enig inzicht in het chemisch gedrag van de olefine-functie in 1 en 2 werd verkregen door deze verbindingen te onderwerpen aan typische olefine-reacties, zoals hydrogenering, bromering en een 1,3-dipolaire cycloadditie met diazomethaan. Hydrogenering van de dubbele binding in 1 tot verbinding 20 kon alleen zonder omlegging van de kooistruktuur plaatsvinden in de aanwezigheid van een kleine hoeveelheid amine. Zonder amine vond voor de eigenlijke hydrogenering een nagenoeg kwantitatieve omzetting naar het carbonyl-brexeen-skelet plaats. Bromering van 1 en 2 in chloroform leidde enkel tot de vorming van complexe mengsels van produkten, waaruit geen identificeerbare verbindingen zijn te isoleren. Wel kon worden vastgesteld, dat omlegging van 1 en 2 tot de corresponderende carbonyl-brexenen vooraf gaat aan de vorming van de complexe mengsels. Een uniek cyclopropyl bevattend lacton 21 werd verkregen bij de bromering van 2 in tetrachloormethaan. Een vergelijkbaar lacton werd niet waargenomen voor 1. De diazomethaan additie aan 1 en 2 en de ermee corresponderende alkoholen en acetaten leidde tot de producten 22. Een duidelijk effect van de carbonyl-functie op de reactiviteit van de olefinische dubbele binding in deze cycloadditie kon worden vastgesteld. De hogere reactiviteit van de carbonyl-brendenen 1 en 2 t.o.v. diazomethaan, in vergelijking met de corresponderende alkoholen en acetaten, kan worden verklaard d.m.v. een "non-bonded" interactie tussen de twee π-functies, die de verbindingen 1 en 2 een "pseudo-enon" karakter geven.



14 n=1
15 n=2



16 Nu = Cl en n = 1
Nu = Br en n = 1,2
Nu = OMe en n = 2



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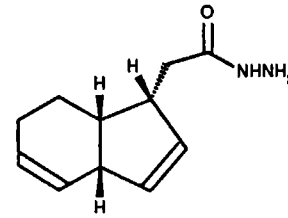

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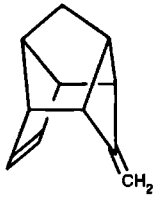

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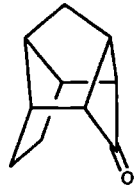

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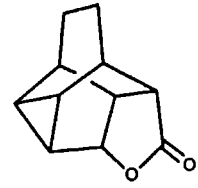

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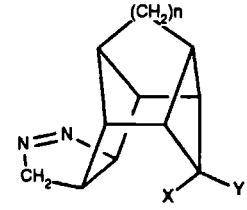
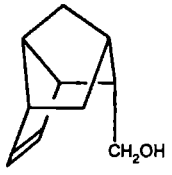


22 X=Y=O; n=1,2
X=OH, Y=H; n=1,2
X=OAC, Y=H; n=1,2

Hoofdstuk 4 is gewijd aan de chemie van de gespannen alkenolen **4** en **5**. Deze alkoholen zijn bijzonder interessant, omdat zij een hydroxyl en olefine functie bezitten die dicht bijelkaar geplaatst zijn. De mogelijkheid van een intramoleculaire additie van het alkoholisch zuurstof atoom aan de niet-geaktiveerde dubbele binding werd onderzocht. Pogingen om deze intramoleculaire nucleofiele additie onder neutrale en basische omstandigheden (natrium methoxide in methanol) te realiseren voor alkenol **4** mislukten. Wanneer een sterkere base werd gebruikt zoals kalium t-butoxide in tertiare butyl alcohol resulteerde dat voor alcohol **4** (R=H) in een cyclobutanon-ringopening met enon **1** en carbinol **23** als de uiteindelijke produkten. Een totaal ander gedrag werd waargenomen voor de alkenolen **5**. Bij een reactie met natronloog in methanol onder reflux-condities werd een probleemloze omzetting in de oxakooi verbindingen **24** waargenomen. Een meer gedetailleerde studie van deze additie reactie toonde aan dat het gebruik van een protisch oplosmiddel essentieel is. Het mechanisme omvat een reversibele deprotonering van de alkoholfunctie gevolgd door een snelheidsbepalende additie van het alkoholaat anion aan de dubbele binding. In de carbanion-achtige overgangstoestand wordt een participatie van het protisch oplosmiddel d.m.v. polarisatie--complexatie aan de *exo*-zijde van het molecuul verondersteld. Deze stereospecifieke *exo*-protonering werd bewezen d.m.v. een D-labeling experiment. De waarneming dat de tertiare alkenolen **5** (R≠H) sneller reageren dan secundair alkenol **5** (R=H) kan worden verklaard door een dichtere nadering van de alkohol en alkeen functie bij de tertiare alkenolen als gevolg van een sterkere pyrimidalisatie van het carbinol-koolstofatoom. De inreactiviteit van de alkenolen **4** kan

worden verklaard op grond van hun hogere rigiditeit die resulteert in een hogere activeringsenthalpie voor de reactie. Dit kon worden bevestigd door Minimum Energy Reaction Path-berekeningen. Intramoleculaire additie van de hydroxylfunctie aan de dubbele binding kon voor **4** (R=H) worden gerealiseerd door activering van de dubbele binding door reactie met broom. De vorming van een bromonium ion in de nabijheid van de dichtbij gesitueerde alcoholfunctie leidt tot een snelle vorming van de oxakooi-verbinding **25**. Deze activering is zo sterk dat zelfs een methylether van **4** (R=H) snel werd omgezet in **25**.



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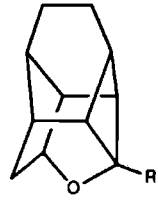
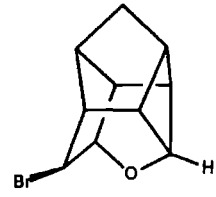


24 R = H, Me, n-Bu, Ph



25

Samenvattend: tetracyclische enonen **1**-**3** zijn intrigerende systemen met twee π-systemen in elkaars nabijheid, waarvan de chemie is geassocieerd met hun gespannen en rigide structuren. De cyclobutanoneenheid is erg gevoelig voor Brönsted en Lewis zuren en legt via een cyclobutyl/cyclopropyl-carbinyl/homoallylisch kation intermediair snel om naar minder gespannen verbindingen. Bij nucleofiele additie reacties blijkt bovendien dat de cyclobutanon-carbonylfunctie een ongewoon lage reactiviteit bezit. De tetracyclische alkoholen **4** en **5** zijn uitstekende modelverbindingen om fundamenteel inzicht te verschaffen in de additie van nucleofielen aan niet-geaktiveerde olefine bindingen.

CURRICULUM VITAE

Hubertus (Bert) L.E. Depré werd geboren op 22 maart 1962 te Kerkrade. Op 30 mei 1980 behaalde hij het diploma Atheneum B aan het Sint Antonius Doctor College te Kerkrade.

In september van hetzelfde jaar startte hij met de studie Scheikunde aan de Katholieke Universiteit Nijmegen. Het doctoraal examen omvatte als hoofdvak Organische Chemie (Prof. Dr. B. Zwanenburg; onderwerp: De synthese en eigenschappen van het tetracyclo[5.3.0.$0^{2,5}$.$0^{4,8}$]decenon, een gespannen structuur met twee orthogonale π-systemen). Het uitgebreide bijvak betrof Molecuulspectroscopie (Prof. Dr. Ir. W.S. Veeman). Op 26 januari 1987 werd het doctoraal-examen behaald.

Vanaf 1 februari 1987 tot 31 januari 1991 was hij werkzaam als assistent in opleiding bij de vakgroep Organische Chemie aan de Katholieke Universiteit Nijmegen. In deze periode werd onder begeleiding van Prof. Dr. B. Zwanenburg en Dr. A.J.H. Klunder, het in dit proefschrift beschreven onderzoek verricht.

Gedurende de gehele opleiding was hij enige malen als assistent betrokken bij de practica Synthese 1 en 2.

Van 1 april 1991 tot 31 augustus 1992 vond hij zijn eerste dienstbetrekking bij Indola Cosmetics Produktiemaatschappij B.V., toendertijd gevestigd in Voorburg. Sedert 1 september 1992 is hij werkzaam bij Intercol B.V. te Ede.